Neonatal Effects of Magnesium Sulfate Given to the Mother

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The history of obstetric use of magnesium sulfate begins with its use during the middle of the 20th century to treat and/or prevent eclampsia or preterm labor. More recently, antepartum magnesium sulfate has been suggested for prevention of cerebral palsy in preterm infants. Although adverse effects and toxicity of magnesium in pregnant women are well known, the fetal-neonatal effects of magnesium are less clear. The objective of this study was to evaluate the effects of magnesium on the newborn infant.

**Objective** Magnesium historically has been used for treatment and/or prevention of eclampsia or preterm labor. More recently, antepartum magnesium sulfate has been suggested for prevention of cerebral palsy in preterm infants. Although adverse effects and toxicity of magnesium in pregnant women are well known, the fetal-neonatal effects of magnesium are less clear. The objective of this study was to evaluate the effects of magnesium on the newborn infant.

**Study Design** This is a retrospective cohort analysis of women who received antepartum magnesium sulfate for prevention or treatment of eclampsia. Magnesium sulfate was given intravenously beginning with a 6-g dose, followed by 2- to 3-g/h infusion. Newborn hypotonia was diagnosed if an infant exhibited less than normal tone/activity upon admission to the nursery.

**Results** Between January 2000 and February 2009, a total of 6654 women with preeclampsia were treated with intravenous magnesium sulfate as described; 88 (6%) of the infants were diagnosed with hypotonia. Lower 1-minute and 5-minute Apgar scores, intubation in the delivery room, admission to special care nursery, and hypotonia were all significantly increased as maternal serum magnesium concentrations increased before birth.

**Conclusion** Several neonatal complications are significantly related to increasing concentrations of magnesium in the maternal circulation.
Maternal Demographics

Between January 1, 2000, and February 1, 2009, a total of 144,715 women were delivered at Parkland Hospital; 7374 women were given magnesium sulfate -7H₂O for intrapartum management of pregnancy hypertension, and 6654 (90%) met inclusion criteria for this analysis.

Serum Magnesium Levels

The distribution of maternal serum magnesium concentrations, duration of magnesium sulfate infusion, as well as the mean number of magnesium levels measured are shown in Table 1. The duration of infusion and number of magnesium levels measured were both significantly related to the serum magnesium level in the mother. That is, higher levels were associated with longer infusions. A total of 139 women had magnesium levels 7.0 mEq/L (3.5 mmol/L) or greater; their mean concentration was 7.7 ± 0.7 mEq/L (3.8 ± 0.35 mmol/L) with a range of 7.1 to 11.0 mEq/L (3.6 to 5.5 mmol/L).

Maternal Demographics

Maternal demographic characteristics for the study cohort are shown in Table 2. The majority of the women were...
Table 1 Maternal Serum Magnesium Levels within 4 Hours of Delivery in 6654 Women as Well as Infusion Times and Number of Serum Levels Measured

<table>
<thead>
<tr>
<th>Magnesium Level (mEq/L)</th>
<th>Outcome</th>
<th>0–3.0 ( (n = 326) )</th>
<th>3.0–3.99 ( (n = 1965) )</th>
<th>4.0–4.99 ( (n = 2572) )</th>
<th>5.0–5.99 ( (n = 1329) )</th>
<th>6.0–6.99 ( (n = 323) )</th>
<th>7.0 or Greater ( (n = 139) )</th>
<th>( p ) Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infusion hours</td>
<td>3.8 ± 4.1</td>
<td>4.1 ± 3.4</td>
<td>8.4 ± 5.1</td>
<td>13.1 ± 6.1</td>
<td>15.7 ± 6.1</td>
<td>19.1 ± 6.7</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>No. magnesium levels</td>
<td>1.5 ± 0.8</td>
<td>1.8 ± 0.9</td>
<td>2.7 ± 1.1</td>
<td>3.6 ± 1.3</td>
<td>4.0 ± 1.2</td>
<td>4.5 ± 1.3</td>
<td>&lt;0.001</td>
<td></td>
</tr>
</tbody>
</table>

All data shown as mean ± standard deviation. 1 mEq/L = 2 mmol/L.

Neonatal Outcomes in Relation to Maternal Serum Magnesium Levels

A variety of neonatal outcomes are shown in Table 3 in relation to maternal serum magnesium concentrations. Gestational age at delivery, mechanical ventilation in the nursery, intraventricular hemorrhage, and neonatal death were not significantly associated with maternal serum magnesium concentrations. In contrast, 1-minute and 5-minute Apgar scores, intubation in the delivery room, admission to special care nursery, and hypotonia were significantly increased as maternal serum magnesium concentrations increased. For example, 12% of infants whose mothers had magnesium levels 7.0 mEq/L (3.5 mmol/L) or greater had hypotonia compared with 3% in those with levels of 3.0 to 3.99 mEq/L (1.5 to 2.0 mmol/L, \( p < 0.001 \)). Similarly, intubation in the delivery room occurred in 5% of infants born to mothers with magnesium levels 7.0 mEq/L (3.5 mmol/L) or greater compared with 2% in women with levels 3.0 to 3.99 mEq/L (1.5 to 2.0 mmol/L, \( p < 0.001 \)). Logistic regression analysis, adjusting for nulliparity, gestational age at birth, and length of labor was performed for hypotonia and intubation in the delivery room. As shown in Fig. 1, the rate of hypotonia was proportional to the maternal serum magnesium level. After adjustment, intubation in the delivery room was significantly associated with maternal magnesium serum levels exceeding 7.0 mEq/L (3.5 mmol/L; odds ratio 4.6, 95% confidence interval 1.4 to 15.4).

Table 2 Maternal Demographic Characteristics in Women with Pregnancy Hypertension and Treated with Magnesium Sulfate Infusions

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Number of Women ( (n = 6654) )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Race/ethnicity</td>
<td></td>
</tr>
<tr>
<td>Hispanic</td>
<td>5217 (78)</td>
</tr>
<tr>
<td>African-American</td>
<td>1063 (16)</td>
</tr>
<tr>
<td>White</td>
<td>286 (4)</td>
</tr>
<tr>
<td>Other</td>
<td>88 (1)</td>
</tr>
<tr>
<td>Age (y)</td>
<td></td>
</tr>
<tr>
<td>≤15</td>
<td>138 (2)</td>
</tr>
<tr>
<td>16–34</td>
<td>5770 (87)</td>
</tr>
<tr>
<td>≥35</td>
<td>746 (11)</td>
</tr>
<tr>
<td>Nulliparity</td>
<td>3580 (54)</td>
</tr>
<tr>
<td>Body mass index*</td>
<td></td>
</tr>
<tr>
<td>≤19</td>
<td>3 (–)</td>
</tr>
<tr>
<td>20–24</td>
<td>328 (5)</td>
</tr>
<tr>
<td>25–30</td>
<td>1533 (23)</td>
</tr>
<tr>
<td>&gt;30</td>
<td>4254 (63)</td>
</tr>
</tbody>
</table>

All data shown as \( n \) (%).

*Data missing in 536 (8%) women.

Discussion

Our analysis indicates that several neonatal outcomes are significantly related to increasing concentrations of magnesium ion in the maternal circulation. Apgar scores, hypotonia, intubation in the delivery room, and admission to a special care nursery were all increased as the maternal magnesium level increased from 3.0 to 7.0 mEq/L (1.5 to 3.5 mmol/L) or greater. The great preponderance of maternal magnesium levels were in the desired therapeutic range of 4.0 to 7.0 mEq/L (2.0 to 3.5 mmol/L); only 33 women (0.5% of the study cohort) had levels exceeding 8 mEq/L (4.0 mmol/L) and the highest level was 9.1 mEq/L (4.6 mmol/L). That is, the neonatal effects of magnesium ion that we observed occurred primarily within the therapeutic range and were not solely attributable to excessive levels of magnesium in the maternal circulation. Although there were several adverse neonatal effects of magnesium sulfate, it is likely that their clinical impact was small because neonatal death and serious morbidities such as need for significant respiratory support in the nursery were not statistically related to maternal magnesium levels. However, we believe that larger prospective trials would be necessary to more completely evaluate the potential adverse effects of neonatal hypermagnesemia.
Our findings of adverse neonatal effects of magnesium sulfate given to the mother are not new. Indeed, Lipsitz and English\textsuperscript{6} reported more than 40 years ago a case series of six infants who had hyporeflexia, hypotonia, and respiratory depression, which was attributed to magnesium sulfate given to the mother. Lipsitz later reported a larger case series including 37 infants in which he found a trend toward lower Apgar scores in association with maternal magnesium sulfate therapy.\textsuperscript{13} Stone and Pritchard\textsuperscript{14} were unable to confirm changes in Apgar scores in 118 infants born of women given magnesium sulfate for prevention of eclampsia. Donovan and colleagues\textsuperscript{15} reported decreased muscle tone in 20 newborn infants associated with maternal magnesium levels. Chesley\textsuperscript{16} found cord blood magnesium levels to be 70 to 96\% of those in the mother with a progressive increase in fetal levels as the duration of maternal magnesium sulfate therapy lengthened. Until very recently, the literature now cited comprised most of the information on the neonatal effects of magnesium sulfate given to the mother. In 2008, Rouse and colleagues\textsuperscript{3} randomized magnesium sulfate infusions or placebo in 2241 women delivered between 24 and 31 weeks’ gestation in a study of the effects of magnesium sulfate on

\begin{table}[h]
\centering
\caption{Selected Neonatal Outcomes in Relation to Maternal Magnesium Levels Measured within 4 Hours of Birth}
\begin{tabular}{|c|c|c|c|c|c|c|}
\hline
\textbf{Magnesium Level (mEq/L)} & \textbf{0–3.0 (n = 326)} & \textbf{3.0–3.99 (n = 1965)} & \textbf{4.0–4.99 (n = 2572)} & \textbf{5.0–5.99 (n = 1329)} & \textbf{6.0–6.99 (n = 323)} & \textbf{7.0 or Greater (n = 139)} & \textbf{p Value} \\
\hline
\textbf{Outcome} & & & & & & & \\
\hline
\textbf{Gestational age (wk)} & & & & & & & \textbf{0.173} \\
\hline
\textbf{24–27} & 4 (1.2) & 9 (0.5) & 11 (0.4) & 5 (0.4) & 1 (0.3) & 1 (0.7) & \\
\textbf{28–33} & 20 (6.1) & 124 (6.3) & 144 (5.6) & 77 (5.8) & 17 (5.3) & 4 (2.9) & \\
\textbf{34–36} & 54 (16.6) & 230 (11.7) & 352 (13.7) & 175 (13.2) & 39 (12.1) & 11 (7.9) & \\
\textbf{≥37} & 248 (76.1) & 1602 (81.5) & 2065 (80.3) & 1072 (80.7) & 266 (82.4) & 123 (88.5) & \\
\hline
\textbf{1-min Apgar} & & & & & & & \textbf{<0.001} \\
\hline
\textbf{Mean ± SD} & 7.8 ± 1.6 & 8.0 ± 1.4 & 7.9 ± 1.5 & 7.7 ± 1.6 & 7.4 ± 1.9 & 6.9 ± 2.3 & \\
\hline
\textbf{≤3} & 13 (4) & 49 (2) & 95 (4) & 51 (4) & 21 (7) & 17 (12) & \textbf{<0.001} \\
\hline
\textbf{5-min Apgar} & & & & & & & \textbf{<0.001} \\
\hline
\textbf{Mean ± SD} & 8.8 ± 0.6 & 8.8 ± 0.6 & 8.8 ± 0.6 & 8.8 ± 0.7 & 8.6 ± 1.0 & 8.5 ± 0.9 & \textbf{<0.001} \\
\hline
\textbf{≤3} & 0 (0) & 3 (0.2) & 5 (0.2) & 1 (0.1) & 3 (0.9) & 0 (0) & 0.779 \\
\hline
\textbf{Intubation in delivery room} & 9 (3) & 36 (2) & 46 (2) & 14 (1) & 6 (2) & 7 (5) & 0.003 \\
\hline
\textbf{Special care nursery} & 78 (24) & 342 (17) & 491 (19) & 279 (21) & 80 (25) & 34 (24) & \textbf{<0.001} \\
\hline
\textbf{Hypotonia} & 12 (4) & 56 (3) & 135 (5) & 112 (8) & 40 (12) & 18 (13) & \textbf{<0.001} \\
\hline
\textbf{Significant respiratory support in the nursery\textsuperscript{a}} & 40 (12) & 163 (8) & 195 (8) & 95 (7) & 29 (9) & 10 (7) & 0.30 \\
\hline
\textbf{Intraventricular hemorrhage} & & & & & & & \\
\hline
\textbf{Any grade} & 7 (2) & 37 (2) & 29 (1) & 23 (2) & 7 (2) & 0 (0) & 0.25 \\
\hline
\textbf{Grades III/IV} & 1 (0.3) & 3 (0.2) & 2 (0.1) & 2 (0.2) & 1 (0.3) & 0 (0) & 0.96 \\
\hline
\textbf{Neonatal death} & 0 (0) & 1 (0.1) & 6 (0.2) & 1 (0.1) & 0 (0) & 0 (0) & 0.62 \\
\hline
\end{tabular}
\end{table}

All data shown as n (%) or mean ± SD. 1 mEq/L = 2 mmol/L. SD, standard deviation.

\textsuperscript{a}Includes intubation or continuous positive airway pressure in the special care nursery.

![Figure 1](image.png)

\textbf{Figure 1} Probability of neonatal hypotonia in relation to maternal serum magnesium concentrations measured within 4 hours of birth. Data adjusted for gestational age, nulliparity, and length of labor. The \(p\) value for association of hypotonia and magnesium level is \(<0.001\). AUC, area under the curve.
perinatal death and/or cerebral palsy at 2 years of age. Magnesium sulfate therapy was not found to be associated with perinatal death, neonatal hypotonia, or any other neonatal morbidities. Such therapy, however, was associated with a significant reduction in cerebral palsy, especially in infants born between 24 and 27 weeks’ gestation.

The increasing, almost ubiquitous use of magnesium sulfate in American obstetrics has not occurred without concerns as to the safety of magnesium sulfate infusions. For example, the Institute of Medicine as well as the Joint Commission on Accreditation of Healthcare Organizations have identified magnesium sulfate as a high-risk medication for pregnant women. Indeed, magnesium sulfate is listed as a “High Alert Medication” by the Institution for Safe Medication Practices. Although recognized as a high-risk medication, the number of maternal adverse drug events is not well documented in the United States. Simpson and Knox, in the span of few years, accumulated 52 cases of accidental maternal overdosage with magnesium sulfate. Clearly, magnesium sulfate infusions pose risks to the pregnant woman. Our results, showing neonatal effects and confirming largely forgotten observations made more than 40 years ago, lead us to conclude that administration of magnesium sulfate to pregnant women has discernible effects on the newborn infant.

References
5 Pearson HA, Wray D. Non-competitive antagonism of calcium by magnesium ions at the K(+) -depolarised mouse neuromuscular junction. Eur J Pharmacol 1993;236:323–326