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Magnesium Sulfate in Severe Perinatal Asphyxia: A Randomized, Placebo-Controlled Trial

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What’s Known on This Subject

Only animal studies have shown beneficial effects of magnesium sulfate in perinatal asphyxia.

What This Study Adds

This is the first placebo-controlled trial that has proved the efficacy of postnatal magnesium sulfate treatment in perinatal asphyxia.

ABSTRACT

OBJECTIVE. The goal was to study whether postnatal magnesium sulfate infusion could improve neurologic outcomes at discharge for term neonates with severe perinatal asphyxia.

METHODS. Forty term (≥37 weeks of gestation) neonates with severe perinatal asphyxia were studied in a prospective, longitudinal, placebo-controlled trial. Patients were assigned randomly to receive either 3 doses of magnesium sulfate infusion at 250 mg/kg per dose (1 mL/kg per dose) 24 hours apart (treatment group) or 3 doses of normal saline infusion (1 mL/kg per dose) 24 hours apart (placebo group). Both groups also received supportive care according to the unit protocol for perinatal asphyxia.

RESULTS. In the treatment group, moderate encephalopathy was present in 35% (7 of 20) of the patients and severe encephalopathy in 65% (13 of 20) of patients at admission. In the placebo group, 40% (8 of 20) of patients had moderate encephalopathy and 60% (12 of 20) of patients had severe encephalopathy. The mean serum magnesium concentration in the treatment group remained at ≥1.2 mmol/L for 72 hours after the first infusion. At discharge, 22% (4 of 18) of infants in the treatment group had neurologic abnormalities, compared with 56% (10 of 18) of infants in the placebo group. Also, neuroimaging (head computed tomography) performed on day 14 yielded abnormal findings for fewer infants in the treatment group than in the placebo group (16% vs 44%). Infants in the treatment group were more likely to be receiving oral feedings (sucking) at discharge than were those in the placebo group (77% vs 37%). Good short-term outcomes at discharge occurred for 77% of the patients in the treatment group, compared with 37% of the patients in the placebo group.

CONCLUSION. Postnatal magnesium sulfate treatment improves neurologic outcomes at discharge for term neonates with severe perinatal asphyxia. Pediatrics 2009;123:e764–e769
treatments of glutamate open NMDA channels, allowing excessive calcium influx into the neurons and inducing irreversible neuronal injury. This secondary phase may last as long as 72 hours.

Magnesium is a naturally occurring NMDA receptor antagonist that blocks neuronal influx of calcium within the ion channels. This block is voltage dependent and is overcome during axonal depolarization, which occurs with hypoxic-ischemia. If the extracellular concentration of magnesium is increased, then this block can be restored. Review of the literature regarding the effects of magnesium after simulated hypoxic-ischemic insults in several animal models revealed beneficial effects in some studies and no effect in others.

Magnesium sulfate is widely used as a tocolytic agent and for suppression of pregnancy-induced hypertension, and it has shown beneficial effects in neonates born to treated women. A collaborative eclampsia trial reported that infants born to mothers who received magnesium sulfate before delivery were less likely to be intubated or to be admitted to ICUs. However, there is a paucity of literature regarding the role of magnesium sulfate in term neonates with perinatal asphyxia, and only 1 study showed beneficial results. We performed a randomized, controlled trial to test whether postnatal magnesium sulfate treatment could improve neurologic outcomes at discharge for term neonates with severe perinatal asphyxia.

METHODS

This was a randomized, placebo-controlled trial conducted in the NICU of Sheri Kashmir Institute of Medical Sciences (Srinagar, India), which is a tertiary-care hospital in northern India. On the basis of our previous study, it was estimated that 40 neonates with moderate/severe HIE needed to be studied to allow detection of a 50% reduction in the rate of adverse outcomes with 80% power. These 40 neonates were born in the obstetric department of Sheri Kashmir Institute of Medical Sciences between September 2004 and August 2006. Infants were enrolled after parental consent was obtained; the study was approved by the hospital ethics committee.

Infants eligible for the study had gestational ages of ≥37 weeks, were <6 hours of age at the time of admission, had HIE (moderate or severe), and had severe perinatal asphyxia, as manifested by 3 of the following 4 criteria: (1) history of fetal distress (late deceleration, loss of beat-to-beat variability, fetal bradycardia, or meconium-stained amniotic fluid), (2) need for immediate neonatal ventilation with a bag and mask or through endotracheal intubation for ≥2 minutes after delivery, (3) 5-minute Apgar score of <6, or (4) base deficit of ≥15 mEq/L or pH of ≤7 in cord blood or admission arterial blood samples within the first hour after birth. Moderate or severe HIE was diagnosed for these neonates when ≥1 sign was present in 3 of the following 6 categories: (1) level of consciousness, that is, lethargy (moderate HIE) or stupor or coma (severe HIE); (2) spontaneous activity decreased (moderate HIE) or absent (severe HIE); (3) tone, that is, hypotonia (moderate HIE) or flaccidity (severe HIE); (4) posture, that is, distal flexion (moderate HIE) or decerebrate state (severe HIE); (5) primitive reflexes, that is, suck weak (moderate HIE) or absent (severe HIE) or Moro reflex incomplete (moderate HIE) or absent (severe HIE); (6) autonomic nervous system, that is, pupils constricted (moderate HIE) or deviated, dilated, or nonreactive to light (severe HIE), bradycardia (moderate HIE) or variable heart rate (severe HIE), or periodic breathing (moderate HIE) or apnea (severe HIE). Patients with severe intrauterine growth retardation, any condition unrelated to asphyxia, age of >6 hours at admission, maternal prenatal magnesium administration, metabolic disorder, chromosomal anomalies, or congenital malformations were excluded from the study.

These infants were assigned randomly, with computer-generated random numbers, to receive either magnesium sulfate infusion (treatment group) or normal saline infusion (placebo group). The investigators and caregivers were blinded to the assignment of patients. The asphyxia score (range: 0–9) described by Portman et al, which is based on fetal heart rate, 5-minute Apgar score, and base deficit during the first hour of life, was used to quantitate the severity of asphyxia, and prevalence rates of multiorgan dysfunction were compared. The score for moderate asphyxia is 5, and that for severe asphyxia is >6.

Infants in both the treatment and placebo groups were nursed on servo-controlled, open-care beds, with skin temperature maintained at 36.5°C. On day 1 of life, 10% dextrose solution was administered as the maintenance intravenous fluid; electrolytes were added from day 2 of life. Only two thirds of the maintenance fluids were administered initially, until the syndrome of inappropriate antidiuretic hormone secretion was ruled out. Electrolyte measurements and renal function tests were performed daily for the first 5 days of life and subsequently depending on the condition of the infant. Respiratory support in the form of oxygen therapy or ventilation was provided as and when needed. Pressor support in the form of dopamine or dobutamine administration was provided as and when needed. The treatment group also received magnesium sulfate infusion at 250 mg/kg per dose (1 mL/kg per dose in 20 mL of 5% dextrose solution) over 1 hour, with 2 additional doses repeated at intervals of 24 hours. The placebo group received 3 doses (1 mL/kg per dose) of normal saline solution in 20 mL of 5% dextrose solution, 24 hours apart.

During the initial 72 hours of life, heart rate, respiratory rate, and oxygen saturation were monitored continuously. Blood pressure was monitored during magnesium sulfate infusion and for the subsequent 24 hours through invasive blood pressure monitoring. Blood pressure was monitored subsequently with a noninvasive blood pressure-monitoring system. Clinical assessments included assessments of the neurologic status at admission and during the stay, the grade of HIE (moderate or severe), the type of respiratory support needed, the presence of seizures, and the time for establishment of full oral feedings through sucking, as well as a neurologic
examination at discharge. The neurologic examination was performed by certified clinicians who were blinded to the group assignment of the patients. Laboratory assessments included measurements of serum magnesium, lactate dehydrogenase, and creatine kinase levels, liver function tests, including measurements of aspartate aminotransferase and alanine aminotransferase levels, electrocardiography, echocardiography, neuroimaging (computed tomography [CT] of the head), and electroencephalography. Serum magnesium levels were concealed from the clinicians caring for these neonates. Electroencephalography was performed initially within 72 hours after admission and was repeated at day 14 to assess normalization or persistence of abnormalities. Any electroencephalogram showing constant low voltage, electrocerebral inactivity, or burst suppression was reported as abnormal. Initial head CT was performed on day 3 of life, to look for hypoattenuation of deep nuclear structures, hemorrhage, or both. Follow-up head CT was performed at 14 days of life, to assess the evolution of initial findings or the appearance of distinct abnormal structures, hemorrhage, or both. Follow-up head CT was reported as abnormal. Initial head CT was performed on day 3 of life, to look for hypoattenuation of deep nuclear structures, hemorrhage, or both. Follow-up head CT was performed at 14 days of life, to assess the evolution of initial findings or the appearance of distinct abnormal signs (>2 focal hypodensities, diffuse hypodensity with or without ventricular effacement, hyperdense lesions in basal ganglia, or encephalomalacia). The serum magnesium levels for the treatment and placebo groups (Table 1). The groups received an initial infusion of either magnesium sulfate or an equal volume of placebo solution, which necessitated intubation and temporary ventilatory support.

Characteristics of the hospital course and the status at discharge are shown in Table 2. The numbers of patients with renal involvement, pulmonary hypertension, hypotension requiring presser support, and hepatic dysfunction (aspartate aminotransferase level of >120 IU and alanine aminotransferase level of >135 IU) were similar for the 2 groups. Two (10%) of 20 patients in the treatment group died during the hospital stay. The 2 patients had severe HIE at admission and underwent ventilation from the time of admission. Both were brain dead at 72 hours of life, and they died on day 5 and day 6 of life. In the placebo group also, 2 (10%) of 20 patients died. One patient died on day 3 of life and another on day 9 of life; both had severe HIE.

Four (22%) of 18 patients in the treatment group had neurologic abnormalities (abnormal neurologic examination results) at discharge, compared with 10 (56%) of 18 patients in the placebo group (odds ratio [OR]: 0.22 [95% confidence interval (CI): 0.05–0.90]; P < .04).

### Results

A total of 70 neonates were screened in 48 months. Thirty neonates were excluded (inclusion criteria not fulfilled for 20 neonates, parents refused to participate for 6 neonates, and other causes for 4 patients). Forty neonates fulfilled the inclusion criteria and constituted the study group. Twenty neonates were assigned randomly to the treatment group and 20 to the placebo group. There were 21 male patients and 19 female patients. There were no differences in gestational age, birth weight, gender, mode of delivery, individual components of the asphyxia score (fetal heart rate, 5-minute Apgar score, and base excess), blood pH, or blood pressure between the treatment and placebo groups (Table 1). The serum magnesium levels for the treatment and placebo groups were comparable at 0 hours, but levels for the treatment group were higher (P < .05) at 1, 23, 25, 47, 49, and 72 hours. In the treatment group, the mean serum magnesium concentration increased from 0.77 mmol/L at 0 hour to 1.5 mmol/L within 1 hour after the first dose, from 1.2 to 2.2 mmol/L within 1 hour after the second dose, and from 1.4 to 2.8 mmol/L within 1 hour after the third dose of magnesium sulfate. Therefore, the mean serum magnesium concentration remained at ≥1.2 mmol/L during the initial 72 hours after the first infusion.

There was no significant difference in mean arterial pressures between the treatment and placebo groups (45.4 ± 4 vs 45.5 ± 4.8 mm Hg) at admission (P > .05). No significant decrease in mean arterial pressure occurred during the first 72 hours of life, during which 3 doses of magnesium sulfate were administered in the treatment group. Two patients in the treatment group developed apnea during the second dose of magnesium sulfate, which necessitated intubation and temporary ventilatory support.

### Table 1 Clinical Characteristics of the Treatment and Placebo Groups at Admission

<table>
<thead>
<tr>
<th></th>
<th>Treatment Group (N = 20)</th>
<th>Placebo Group (N = 20)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight, mean ± SD, g</td>
<td>2745 ± 455</td>
<td>2835 ± 539</td>
<td>.56</td>
</tr>
<tr>
<td>Gestation, mean ± SD, wk</td>
<td>38.5 ± 1.5</td>
<td>39 ± 1.2</td>
<td>.49</td>
</tr>
<tr>
<td>Cesarean delivery, n (%)</td>
<td>11 (55)</td>
<td>12 (60)</td>
<td>.74</td>
</tr>
<tr>
<td>Meconium-stained amniotic fluid, n (%)</td>
<td>10 (50)</td>
<td>7 (35)</td>
<td>.33</td>
</tr>
<tr>
<td>Male, n (%)</td>
<td>12 (60)</td>
<td>9 (45)</td>
<td>.11</td>
</tr>
<tr>
<td>Initial arterial blood gas values</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>pH, mean ± SD</td>
<td>7.0 ± 0.13</td>
<td>7.0 ± 0.14</td>
<td>.8</td>
</tr>
<tr>
<td>Base excess, mean ± SD, mEq/L</td>
<td>−18.5 ± 1.5</td>
<td>−18 ± 1.6</td>
<td>.1</td>
</tr>
<tr>
<td>Asphyxia score of &gt;5, n (%)</td>
<td>16 (80)</td>
<td>17 (85)</td>
<td>.8</td>
</tr>
<tr>
<td>Age at first infusion of magnesium sulfate or placebo, mean ± SD, h</td>
<td></td>
<td></td>
<td>.84</td>
</tr>
<tr>
<td>Mean arterial pressure at 12 h of admission, mean ± SD, mm Hg</td>
<td>45.4 ± 3.77</td>
<td>45.5 ± 4.8</td>
<td>.66</td>
</tr>
<tr>
<td>Encephalopathy, n (%)</td>
<td>Moderate</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>7 (35)</td>
<td>8 (40)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Severe</td>
<td>13 (65)</td>
<td>12 (60)</td>
</tr>
</tbody>
</table>
Neuroimaging (head CT) results were abnormal for 16% of patients (3 of 18) in the treatment group, compared with 44% (8 of 18) in the placebo group (OR: 0.25 [95% CI: 0.05–1.17]; P = .07) on day 14 of life. Abnormal CT findings included basal ganglia injury (2 patients in the treatment group and 3 patients in the control group), cortical injury (1 patient in the treatment group and 2 patients in the control group), and injury to both cortical and subcortical areas (3 patients in the control group). Electroencephalographic abnormalities were seen for 22% (4 of 18) of patients in the treatment group, compared with 33% (6 of 18) of patients in the placebo group (OR: 0.57 [95% CI: 0.12–2.5]). Feedingswere initiated by the seventh day for 55% (10 of 18) of patients in the treatment group, compared with 33% (6 of 18) of patients in the placebo group. At discharge, 14 (77%) of 18 patients in the treatment group were receiving oral feedings (sucking), compared with 38% (7 of 18) of patients in the placebo group. Abnormal CT findings at day 14 were seen for 77% (14 of 18) in the treatment group, compared with 37% (7 of 18) in patients in the placebo group (OR: 5.5 [95% CI: 1.2–23.6]; P < .02).

DISCUSSION

Our study shows that postnatal magnesium sulfate treatment improves neurologic outcomes at discharge for term neonates with HIE. Magnesium sulfate is neuroprotective because Mg²⁺ ions gate the NMDA receptor, thereby reducing the Ca²⁺ influx that can trigger cell death. However, this block is voltage dependent and is overcome during the axonal depolarization that occurs with hypoxic-ischemia. If the extracellular magnesium concentration is increased, then this blockade can be restored. In our study, the mean serum magnesium concentration remained at ≥1.2 mmol/L, which is in the therapeutic range. Furthermore, we used 3 doses of magnesium sulfate (250 mg/kg per dose), 24 hours apart, because secondary neuronal injury can last as long as 72 hours.

Postnatal magnesium sulfate infusion was neuroprotective in our study. This was reflected by fewer neonates with neurologic abnormalities and more infants receiving oral feedings at discharge in the treatment group. However, the neuroimaging results were not significant. This could be attributable to the small number of patients. Also, the best neuroimaging modality for HIE is MRI (diffusion-weighted images), and that modality was not available to our patients during the study period. Because MRI of the brain is more sensitive and specific than CT in HIE, more infants with abnormal neuroimaging results likely would have been identified with that modality.

The overall mortality rate in our study was 10%. The mortality rate for our patients was lower than that in previously published studies, and the most likely reason is that life support was withdrawn for no infant. Also, the number of patients was too small to enable evaluation of a significant effect of magnesium sulfate on survival rates. Although we did not observe any decrease in blood pressure during or after magnesium sulfate infusion, 2 of our patients developed apnea and required ventilation, which confirms that adverse effects can occur during infusion and intense monitoring is needed.

The entry criteria for our study consisted of clinical and biochemical parameters and did not include the use of amplitude-integrated electroencephalography. In our study, however, a very high-risk population was included on the basis of clinical, biochemical, and neurologic criteria, as confirmed by 4 deaths, the need for mechanical ventilation immediately after birth for 23 patients, 14 patients surviving with neurologic abnormalities, and 11 patients with abnormal CT findings at discharge.
The protective role of magnesium sulfate has been based largely on studies with animal models, many of which showed favorable results in terms of amelioration of secondary neuronal injury.13–15 A few studies with pregnant women showed beneficial effects for neonates also. Nelson and Grether26 observed a lower incidence of cerebral palsy in preterm infants born to mothers who had received magnesium sulfate before delivery. Schendel et al18 observed the relationship of intrapartum magnesium sulfate administration to mothers and cerebral palsy in newborns. They showed significant effects of magnesium sulfate in preventing cerebral palsy. Harrison et al28 reported lower incidences of fetal heart rate deceleration and term stillbirths for mothers who received magnesium supplementation during pregnancy. However, there was no effect on the incidence of HIE, because it was an underpowered study and compliance was poor among the study population.

There has been only 1 postnatal human trial regarding the role of magnesium sulfate in neonates with perinatal asphyxia.19 The study showed good outcomes among patients treated with magnesium sulfate in the immediate neonatal period. However, it was not a placebo-controlled trial. Our study is the first placebo-controlled trial that shows improved neurologic outcomes at discharge in the magnesium sulfate group. Good short-term outcomes at discharge, the composite measure of all parameters, were statistically significant (P < .02), although individual components except neurologic abnormalities and oral feeding (sucking) were not significant (because of the small number of patients).

The role of magnesium sulfate in neuroprotection also is being evaluated in acute traumatic brain injury, in both adults and children. In a recent study, magnesium sulfate administration to children with severe traumatic brain injuries did not decrease cerebral perfusion pressure or mean arterial pressure and had no adverse effects on cardiac conduction.29 Although 1 study in adults showed no beneficial effects of magnesium sulfate after traumatic brain injury,30 many other studies are being conducted to test the neuroprotective abilities of magnesium sulfate in acute trauma.

CONCLUSIONS
Postnatal magnesium sulfate infusion is effective in improving outcomes for infants with severe perinatal asphyxia when it is given early (within 6 hours) and, in combination with other modalities of treatment (hypothermia) during the therapeutic window, it could be very beneficial. However, more studies with larger sample sizes, preferably multicenter trials, are needed to confirm the results.

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