Magnesium Sulfate and Novel Therapies to Promote Neuroprotection

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**INTRODUCTION**

Preterm delivery (PTD) is a major cause of neonatal morbidity and mortality, with surviving infants at risk for long-term neurologic sequelae. Although any birth occurring before the completion of 37 weeks’ gestation is considered preterm, most serious harm occurs in the 16% of preterm deliveries occurring before 32 weeks’ gestation.\textsuperscript{1} Neurodevelopmental impairments can include cerebral palsy (CP), cognitive dysfunction, and sensory impairments (blindness and deafness). Cerebral palsy affects 2 per 1000 infants; however, the risk of CP is inversely proportional to gestational weight and age at delivery. Thus, the prevalence of CP is increased to 60 per 1000 infants in neonates weighing less than 1500 g\textsuperscript{2}; and approximately one-third of new CP cases are associated with delivery before 32 weeks’ gestation.\textsuperscript{3} Within the spectrum of neurologic impairment associated with PTD, CP has been used as the primary

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**KEYWORDS**

- Magnesium sulfate
- Neuroprotection
- Cerebral palsy

**KEY POINTS**

- Magnesium sulfate has been shown to reduce the risk of moderate to severe cerebral palsy when given before delivery before 32 weeks’ gestation.
- Magnesium sulfate has been long studied and has an excellent safety profile.
- The authors recommend a bolus followed by continuous dosing of magnesium in pregnancies at risk of delivery before 32 weeks’ gestation until delivery occurs or is no longer imminent.
- Novel therapies for neuroprotection include therapeutic hypothermia, remote ischemic preconditioning, xenon, argon, creatine, stem cells, and other neuromodulators.

**INTRODUCTION**

Preterm delivery (PTD) is a major cause of neonatal morbidity and mortality, with surviving infants at risk for long-term neurologic sequelae. Although any birth occurring before the completion of 37 weeks’ gestation is considered preterm, most serious harm occurs in the 16% of preterm deliveries occurring before 32 weeks’ gestation.\textsuperscript{1} Neurodevelopmental impairments can include cerebral palsy (CP), cognitive dysfunction, and sensory impairments (blindness and deafness). Cerebral palsy affects 2 per 1000 infants; however, the risk of CP is inversely proportional to gestational weight and age at delivery. Thus, the prevalence of CP is increased to 60 per 1000 infants in neonates weighing less than 1500 g\textsuperscript{2}; and approximately one-third of new CP cases are associated with delivery before 32 weeks’ gestation.\textsuperscript{3} Within the spectrum of neurologic impairment associated with PTD, CP has been used as the primary
measurable outcome variable in most of the clinical studies evaluating neuroprotection strategies.

The International Committee on Cerebral Palsy Classification defines CP as a group of developmental disorders of movement and posture causing activity limitations that can be attributed to nonprogressive disturbances occurring in the developing fetal or infant brain. The motor disorders seen in CP are often seen with additional sequelae, such as changes in cognition, communication, perception, sensation, behavior, or seizures. Approximately one-third of cases of CP are associated with delivery before 32 weeks’ gestation. Although the pathophysiology of CP is complex, it is thought to be mediated by inflammation, most often combined with impaired oxygen delivery to the fetal brain leading to decreased ATP level, increased lactic acid level, and damage to neurons, myelin, plasticity, and cell death. These intrauterine insults can lead to long-term neurologic damage. Risk factors include prematurity, multiple gestation, intrauterine growth restriction, intracranial hemorrhage, infection, placental disorder, genetic syndromes, structural brain anomalies, birth asphyxia, trauma, and kernicterus. Significant overlap and confounding can occur with these variables as seen in premature infants.

The Centers for Disease Control and Prevention (CDC) estimated the direct lifetime cost of CP to exceed $2 billion dollars in 2003. Indirect costs associated with CP are approximately 7-fold to 8-fold higher than direct costs. Lifetime costs to the individual consist of medical and indirect costs and productivity losses, which were estimated to be approximately $921,000 per person with CP in 2003. Caregivers and family members are also strongly affected by having a child with CP, dependent on the child’s behavioral issues, caregiving, demands, and family function, which can have lasting effects on their physical and mental health. These enormous economic and societal costs, direct and indirect, underscore the need for effective primary and secondary prevention measures. Moreover, economic evaluation has shown the cost-effectiveness of prevention efforts.

This article reviews pharmacologic therapies and strategies used for neonatal neuroprotection. The capacity of magnesium sulfate (MgSO4) to mediate neuroprotection has been investigated within multiple clinical trials using different protocols and inclusion criteria, and the salient differences between the cohorts, protocols, and results are considered. Using this information, this article reviews pharmacokinetic modeling that is helpful in considering refined MgSO4 protocols for neuroprotection. It also discusses novel therapies in place for the prevention of CP (Box 1). Given the societal cost of neonatal neurologic injury, in the setting of a stable preterm birth rate, additional studies are required to identify and confirm other neuroprotective agents and to determine the most effective regimens to use.

**PHARMACOLOGIC INTERVENTIONS**

**Magnesium Sulfate**

Magnesium sulfate has been widely used in the obstetric environment for several decades. Historically used as a tocolytic agent and to prevent and treat eclampsia, magnesium was noted to potentially decrease the incidence of CP and intraventricular hemorrhage in exposed infants following maternal administration. Although MgSO4 remains the treatment of choice for women with eclampsia, the utility of magnesium as a tocolytic remains controversial. A 2002 Cochrane analysis concluded that MgSO4 was not effective at preventing preterm birth. It is relevant to note that only 3 of the 23 analyzed trials included placebo groups (99 placebo subjects in total) in which magnesium therapy was compared with
no alternative tocolysis, with the investigators acknowledging sparse data of “generally poor quality.” After publication of this meta-analysis, MgSO₄ use for tocolysis in the United States declined, with at least 1 small study and published commentary suggesting magnesium was ineffective and potentially even dangerous. The increasing use of MgSO₄ as a neuroprotective agent followed the publication of clinical trials, meta-analyses, and recommendations largely within the last decade.

**Mechanism of action**

Magnesium is a micronutrient involved in a multitude of biochemical and physiologic pathways. Magnesium plays a role in energy metabolism, nucleic acid synthesis, regulation of adenylate cyclase, transmembrane ion flux, muscle contraction, vasomotor tone, cardiac excitability, neuronal activity, and neurotransmitter release. Its mechanism of action in the obstetric milieu is poorly understood. Related to its role as a tocolytic, magnesium competes with calcium at the motor end plate at the myometrial cell membrane, therefore reducing myometrial cell excitation and preventing contraction. Our laboratory has shown that magnesium reduces inflammatory cytokine production and nuclear factor kappa-B (NF-KB) activation. Inflammation and infection are closely linked to preterm parturition, thus this activity could account in part for the utility of magnesium as a tocolytic therapy.

Magnesium is also a smooth muscle relaxant, potentially affecting cerebral endothelium forming the blood-brain barrier. Magnesium may also influence neurologic function via its role as an N-methyl-D-aspartate (NMDA) antagonist. Stimulation of NMDA receptors by neurotransmitters such as glutamate may lead to seizures when neuronal networks are overactivated. One hypothesis is that magnesium prevents eclamptic seizures by inhibiting NMDA receptors. NMDA inhibition may also reduce ischemia-associated neuronal damage; these proposed neuroprotective mechanisms are supported by work in preclinical animal models. Magnesium’s antinflammatory properties may also ameliorate ischemia-associated damage and reduce seizure activity via NMDA inhibition and a reduction in NF-KB activation.

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**Box 1**

Emerging therapies

- **Pharmacologic**
  - Erythropoietin
  - Darbepoetin
  - Bone marrow derived and mesenchymal stem cells
  - Vasopressin
  - Endocannabinoids
  - Melatonin
  - Xenon
  - Argon
  - Allopurinol
  - Topiramate
  - Creatine

- **Non-pharmacologic**
  - Delayed cord clamping
  - Cord milking
  - Therapeutic hypothermia
  - Remote ischemic preconditioning
Pharmacokinetics
Magnesium (Mg\(^{2+}\)), a divalent cation, is the fourth most common cation in humans, with SO\(_4^{2-}\) being the complementary anion moiety of the clinically used compound. Magnesium is almost exclusively intracellular, with only 1% of total body magnesium found extracellularly. Serum Mg\(^{2+}\) accounts for 0.3% of total body content, and circulating levels decrease during pregnancy from 0.75 to 0.95 mM to 0.54 to 0.90 mM secondary to physiologic hemodilution. Intrapartum magnesium is typically administered intravenously, with some hospitals using intramuscular administration. Myometrial contractility is inhibited with serum Mg\(^{2+}\) levels between 5 and 8 mg/dL. Loss of deep tendon reflexes is noted with serum levels between 9 and 13 mg/dL, although there can be individual variability and subjectivity in this assessment. Respiratory depression is seen with serum Mg\(^{2+}\) levels of 14 mg/dL or greater (Fig. 1). Calcium gluconate is used to treat magnesium toxicity in the setting of respiratory depression. Neonatal Mg\(^{2+}\) levels correlate with cumulative received dose. Magnesium is excreted by the kidneys and has a half-life of less than 3 hours.

Confounders
Clearance rates have been studied in patients receiving MgSO\(_4\) for seizure prophylaxis, preterm labor, and extreme prematurity. A recent pharmacokinetic study investigated the covariates gestational age, presence of preeclampsia, maternal weight, antepartum versus postpartum status, and maternal creatinine in MgSO\(_4\) administered for neuroprotection with a 4-g loading dose followed by maintenance dose of 2 g/h. In this study, 111 maternal subjects with 687 magnesium levels and 66 umbilical cord blood levels were analyzed. Preeclampsia status and maternal weight significantly influenced magnesium pharmacokinetics (P values <.001). The half-life of magnesium was 2.7 hours in nonpreeclamptic women and 3.9 hours in preeclamptic women. Steady-state calculations in women were additionally affected by preeclampsia status and were 5.1 mg/dL compared with 7.2 mg/dL in women without and with preeclampsia, respectively. Maternal weight also affected serum MgSO\(_4\) levels, with increasing maternal weight associated with a longer time to steady state. Maternal body weight differences are theorized to be influenced by volume distribution alterations because most of pregnancy weight gain is extracellular body water. Gestational age, antepartum versus postpartum status, and maternal creatinine did not influence MgSO\(_4\) pharmacokinetics in this investigation.

Side effects
Maternal side effects, including hypotension, tachycardia, respiratory depression, discomfort, headache, dizziness, mouth dryness, and blurred vision, have been shown to double with MgSO\(_4\) exposure. Other common side effects, such as nausea/vomiting, flushing, warmth, and sweating, can be increased up to 5 times the baseline rate, whereas itching, tingling, and muscle weakness are increased up to 15 times. Lower dose regimens may decrease side effects, and lengthening

Fig. 1. Serum magnesium levels associated with effect and toxicity.
the loading dose (bolus) time can decrease flushing and feelings of warmth. Overall, maternal side effects secondary to MgSO₄ exposure are mild and readily tolerated. Antepartum MgSO₄ exposure is not associated with serious neonatal effects, including neonatal intensive care unit admission, cardiac or respiratory arrest, or death. Effects of MgSO₄ on the fetal/neonatal brain are not as well known. Neuroneuroprotection is thought to be related to decreased NMDA receptor excitotoxicity, reduced proinflammatory cytokine levels, and oxidative stress. Serious neonatal complications are uncommon with exposure of less than 48 hours and may include lethargy, hypotonia, and respiratory depression. Prolonged MgSO₄ administration is associated in rare instances with neonatal bone demineralization, neonatal hypermagnesemia and hypocalcemia, and maternal osteopenia. These outcomes have been shown with much longer exposure than patients typically receive, in 1 study with cumulative doses ranging from 4400 to 5500 g.43

### Magnesium sulfate for neuroprotection

Multiple randomized controlled clinical trials using MgSO₄ reported long-term outcomes between 2002 and 2008. Although these studies did not meet statistical significance with regard to their primary outcome (Table 1), they were larger and more comprehensive than previously published studies, and collectively they showed that MgSO₄ exposure significantly decreases the likelihood of CP. The Australasian Collaborative Trial of Magnesium Sulfate (ACTOMgSO₄) study showed a decreased incidence of CP from 8.2% in the untreated group to 6.8% in the group receiving MgSO₄ for neuroprotection in patients before 30 weeks’ gestation at risk of preterm delivery, although this was not statistically significant. The Beneficial Effects of Antenatal Magnesium Sulfate (BEAM) trial showed a statistically significant decrease in moderate and severe CP in patients treated with MgSO₄, from 3.5% to 1.9%, respectively. In the PREterm brain protection by MAGnesium sulfate (PREMAG) trial, the rate of combined death or gross motor dysfunction was

### Table 1

**Summary of largest magnesium sulfate neuroprotection trials**

<table>
<thead>
<tr>
<th>Trial</th>
<th>Criteria and Characteristics</th>
<th>Outcomes</th>
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<tbody>
<tr>
<td><strong>BEAM</strong></td>
<td>Time to birth: median 25 h, IQR = 11–63 h</td>
<td>Outcome: stillbirth or infant death, moderate or severe CP at or beyond 2 y of age</td>
</tr>
</tbody>
</table>
| Rouse et al,22 2008 | Average GA = 28.3 ± 2.5 wk  
 n = 2336 |  |
| | Inclusion criterion: GA 24-0/7 to 31-6/7 wk  
 | Exclusion criteria: >8 cm dilated or delivery expected within 2 h |  |
| **ACTOMgSO₄** | Time to birth: median 3.7 h, IQR = 1.4–13.8 wk | Outcome: death, CP, or death or CP at 2 y of age |
| Crowther et al,20 2003 | Mean GA: 27–3/7 wk, IQR 25-5/7 to 28-5/7 wk  
 n = 1062 |  |
| | Inclusion criterion: GA ≤ 30 wk  
 | Exclusion criterion: prior magnesium exposure |  |
| **PREMAG** | Time to birth: median 1.6 h, IQR 0.08–25.08 wk | Outcome: severe white matter injury or death before discharge |
| Marret et al,21 2007 | Median GA: 30–1/7 wk  
 n = 573 |  |
| | Inclusion criterion: GA ≤ 33 wk |  |

*Abbreviations: ACTOMgSO₄, Australasian Collaborative Trial of Magnesium Sulfate; BEAM, Beneficial Effects of Antenatal Magnesium Sulfate; GA, gestational age; IQR, interquartile range.

*Statistically significant (only obtained for 2’ outcome).

*Data from Refs.20-22
decreased from 30.8% to 25.6% with MgSO4 treatment of neuroprotection in children at 2 years of age.\textsuperscript{21} Initially, PREMAG did not show any difference in mortality or severe CP at hospital discharge in infants delivered before 33 weeks’ gestation. Early meta-analyses led to recommendations by the American College of Obstetricians and Gynecologists (ACOG) endorsing the use of MgSO4 for neuroprotection.\textsuperscript{23–25,31} Based on individual participant data meta-analysis, the number needed to treat (NNT) to prevent 1 case of CP in surviving infants is 46; considering only trials with neuroprotective intent, the NNT is 43. These findings are independent of preterm delivery, gestational age, or the cumulative dose amount.\textsuperscript{29}

\textbf{American College of Obstetricians and Gynecologists recommendations}

The ACOG Committee on Obstetric Practice concluded in 2010 that available cumulative evidence suggests that magnesium reduces the risk of CP.\textsuperscript{25} However, the 3 published clinical trials that the recommendations were based on used different treatment regimens (Table 2), so the committee recommended physicians using MgSO4 for neuroprotection develop guidelines regarding inclusion criteria, treatment regimens, concurrent tocolysis, and monitoring in accordance with one of the larger clinical trials. A later ACOG practice bulletin concluded that there is level A evidence suggesting that MgSO4 reduces severity and risk of CP when delivery before 32 weeks’ gestation is anticipated. It further advised that hospitals electing to provide MgSO4 for fetal neuroprotection should develop uniform, specific guidelines addressing inclusion criteria, treatment regimens, concurrent tocolysis, and monitoring in accordance with one of the larger clinical trials.\textsuperscript{45} ACOG Committee Opinion No. 455 (Magnesium Sulfate Before Anticipated Preterm Birth for Neuroprotection) was reaffirmed in 2018 without refinement of the existing recommendations.

\textbf{Evidence and controversies}

There is no consensus on specific MgSO4 dosing. Each of the previously discussed large clinical trials (ACTOMgSO4, PREMAG, and BEAM) used a different protocol with unique inclusion and exclusion criteria. Moreover, query of clinicaltrials.gov does not identify registered trials investigating different dosing protocols. ACOG recommended that physicians develop specific guidelines in accordance with one of the larger published trials.\textsuperscript{25} However, differences between the published trials’ criteria and treatment regimens (see Table 2), combined with real-life heterogeneity in patient presentations, poses an ongoing challenge. Bain and colleagues\textsuperscript{27} acknowledged this

<table>
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<th>Table 2</th>
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<td><strong>Dosing regimens from the largest magnesium sulfate neuroprotection trials</strong></td>
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<tr>
<td>Study</td>
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<tr>
<td>BEAM</td>
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<td>Rouse et al,\textsuperscript{22} 2008</td>
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<td>ACTOMgSO4</td>
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<td>Crowther et al,\textsuperscript{20} 2003</td>
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<td>PREMAG</td>
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conundrum and knowledge gaps in their Cochrane Intervention Review, providing 2 interim neuroprotection recommendations for regimens based on (1) published guidelines from the Australian and Canadian Medical Associations and (2) opinion articles. These recommendations (Table 3) are distinct from protocols used within the published clinical trials, thereby further expanding the array of endorsed neuroprotective regimens.26,27

Given the absence of consensus regarding optimal magnesium dosing for neuroprotection, there have been multiple secondary analyses of existing data and small follow-up studies. A recent individual participant data meta-analysis found minimal variation in outcomes related to time to birth and dosage. Unable to confirm significant benefit with longer administration or higher dosage, it stated that “it would be prudent to restrict administration of antenatal magnesium for fetal neuroprotection to close to the expected or planned birth and to use 4 g, the smallest effective dose, with or without a 1 g/hour maintenance dose.”29 This conclusion is surprising, because it is not supported by a previously published Cochrane meta-analysis performed by many of the same investigators, in which maintenance dosing was associated with reduced CP risk (relative risk [RR], 0.68; 95% confidence interval [CI], 0.51–0.91).24

In this earlier meta-analysis, a 6-g loading dose and higher dose maintenance were also associated with reduced CP risk (RR, 0.59; 95% CI, 0.40–0.85) and retreatment (permitted only in the BEAM trial) was associated with a further decreased risk ratio of CP of 0.68 (95% CI, 0.54–0.87).24

Using data from the BEAM cohort,40 a model was developed to help predict the optimal serum magnesium concentrations for neuroprotection, incorporating the influence of preeclampsia status and maternal weight. Using maternal serum and umbilical cord blood levels, simulated concentrations at delivery were modeled based on the observed pharmacokinetics and pharmacodynamics for patients receiving MgSO4 or placebo within 12 hours of delivery. In this secondary analysis, there was a statistically significant difference between the two groups, with 23 cases of CP in the MgSO4 group (n = 636, 3.6%) and 81 cases of CP in the placebo group (n = 1269, 6.4%).40 In normotensive women, the lowest probability of delivering an infant with CP in the study was associated with a serum magnesium level of 4.1 mg/dL, with a target range 3.7 to 4.4 mg/dL. However, only 23 cases of CP occurred in women receiving MgSO4, and there was no dose-response relationship observed when comparing MgSO4 serum levels and CP rates or severity. There also seemed to be

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<th>Table 3</th>
<th>Recommended regimens for antenatal magnesium sulfate before very preterm birth for neuroprotection of the fetus</th>
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<td><strong>Recommended Regimens</strong></td>
<td><strong>Loading Dosage</strong></td>
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<tr>
<td>Australian National Practice Guidelines, Canadian Clinical Practice Guidelines</td>
<td>4 g over 20–30 min</td>
</tr>
<tr>
<td>Reeves et al,26 2011</td>
<td>6 g over 20–30 min</td>
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no benefit of MgSO₄ neuroprotection in the setting of intrapartum infection. In this model, duration of magnesium administration seems to be predictive of neuroprotection outcomes, with the greatest reduction in CP noted in those receiving greater than 18 hours of MgSO₄ compared with those who received 12 to 18 hours (8.8% vs 11.7%, respectively), although the primary clinical study was not sufficiently powered to determine statistical significance for this outcome. This model predicts that an average-weight woman would achieve the target serum magnesium level of 4.1 mg/dL in 5.5 hours, whereas it may take up to 3 times longer in obese women.⁴⁰

Antibiotics

A recent Cochrane systematic review assessing antepartum and intrapartum interventions for the prevention of CP found that there was an increase in CP in children born to mothers in preterm labor with intact membranes who received prophylactic antibiotics (RR, 1.82; 95% CI, 0.99–3.32).³⁰ This RR was based on a single randomized controlled study including 3173 children. Based on the calculated RR, they concluded that prophylactic antibiotics given to women with intact membranes in preterm labor is probably an ineffective intervention with moderate-quality evidence of harm.³⁰

CLINICAL MANAGEMENT RECOMMENDATION

Differing protocols for MgSO₄ administration used by the recently published studies, combined with a plethora of secondary analyses, have left obstetrics without an evidence-based standard approach to provide intrapartum magnesium for neuroprotection. Based on our opinion, following careful review of published cohort studies using MgSO₄, the most effective neuroprotection strategy is to provide women in preterm labor (or anticipated to deliver within 12 hours) an MgSO₄ bolus followed by continuous dosing until delivery or until the potential for imminent delivery has dissipated. This load (bolus) and maintenance strategy has been used for multiple decades to provide tocolysis and prevent and treat eclampsia, and has been shown to be safe. Furthermore, women receiving MgSO₄ in these earlier trials were also noted to have higher levels of neuroprotection, although this was not statistically significant in the BEAM cohort. Therefore, a continuous dose until delivery or until arrest of preterm labor may be more beneficial in preventing CP. The authors recommend provision of bolus and maintenance-dose MgSO₄ to all women with a pregnancy less than 32 weeks’ gestation at risk for imminent delivery, in the absence of absolute maternal contraindications. Although clinical trials excluded women in the second stage of labor (ACTOMgSO₄) or those expected to deliver within 2 hours (BEAM), the authors think that MgSO₄ for neuroprotection should be offered to all women at risk, given its recognized maternal safety profile, acknowledging that reduced exposure time could limit neuroprotection.

Continuous magnesium infusion is supported by studies showing that cellular magnesium levels equilibrate rapidly.³² Therefore, effectiveness could be limited if magnesium is not present at levels associated with protection at the time of parturition. The rapid clearance rate in normotensive women also supports the concept and safety of retreatment, as does the finding that retreatment was associated with a decreased risk ratio of CP (RR, 0.68; 95% CI, 0.54–0.87).²⁴ Pharmacokinetic modeling suggesting it can take between 5.5 and 18 hours for maternal serum magnesium to reach the theoretic optimal levels also supports the concept of dosing by continuous infusion.

Although the literature also does not reflect consensus regarding the dosing of MgSO₄ for neuroprotection, personal experience, research, and review of the
literature describing MgSO₄ use, pharmacokinetics, and patient outcome, including the prevention of neonatal neurologic injury, prompts our proposal of clinical management recommendations. For normotensive women, we recommend MgSO₄ administration consistent with the higher end of the published neuroprotection protocols, a 6-g loading dose followed by a 2 g/h maintenance dose, based on published predictive models (Fig. 2). This recommendation is grounded on the demonstrated safety of magnesium and on evidence showing that women receiving MgSO₄ for neuroprotection have higher clearance rates than women receiving magnesium in the setting of preeclampsia. It follows that this higher dose would also achieve optimal serum magnesium levels more rapidly in the obese population. An abundance of data show an absence of serious side effects, including maternal intensive care unit admission, respiratory/cardiac failure, or death, in the large cohorts of women who received MgSO₄ for neuroprotection when at risk for delivery before 32 weeks’ gestation in the published clinical trials. In women with preeclampsia and hypertensive disorders, the authors recommend the lower range of dosing used in the clinical cohorts. Our proposed dosing schedule is based on the current status of the literature within and beyond obstetrics, as well as clinical experience and published research from our laboratory and others.

PHARMACOLOGIC THERAPIES UNDER CLINICAL INVESTIGATION

Emerging medical therapies are being tested to help prevent CP at delivery. In broad categories, these include medications designed to increase oxygen supply to the brain using red blood cells or stem cells, neuromodulators, cell membrane stabilizers, and therapies combining different mechanisms of action.

**Erythropoietin and Darbepoetin**

These hormones are known to act to increase the number of circulating red blood cells, thereby increasing oxygen carrying capacity and neurogenesis. Moreover, iron

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**Fig. 2.** Algorithm for MgSO₄ administration with neuroprotective intent. Loading doses are administered over 30 minutes, with continuous intravenous infusion until delivery or threat of imminent delivery subsides. GA, gestational age.
plays a key role in nerve fiber myelination. Evidence from cord milking and delayed cord clamping studies provides indirect proof of concept as to why these medications may mediate neuroprotection. The ongoing Mild Encephalopathy in the Newborn Treated With Darbepoetin (MEND) trial is currently studying the protective effect of darbepoetin.\(^\text{10}\)

**Bone Marrow and Mesenchymal Derived Stem Cells**

Cellular therapies have been trialed as well and are thought to work by decreasing inflammation and oxidative stress and enhancing regeneration.\(^\text{10}\) Experimental animal models have shown that this occurs through various mechanisms using umbilical cord blood cells derived from both bone marrow–derived mesenchymal stem cells (MSCs) and umbilical cord blood–derived MSCs.\(^\text{46}\) Both of these MSCs exhibit paracrine effects secreting trophic and immunomodulatory factors that help in brain injury repair. One model of preterm global hypoxic injury showed that intravenous mesenchymal stem cells induced T-cell tolerance.\(^\text{47}\) Stem cell therapies are the subject of active clinical trials and have shown much potential with a satisfactory safety profile.\(^\text{48}\)

**Postnatal Magnesium Sulfate**

Magnesium sulfate may also be helpful in neonates postdelivery, although there is inconsistent benefit and little consensus in dose and timing. There is a risk of hypotension and bradycardia with MgSO\(_4\), similar to that seen with placental exposure before delivery.\(^\text{10}\)

**EMERGING PHARMACOLOGIC THERAPIES**

Several different neuromodulators are currently being studied in both animal and early human trials. These include vasopressin, endocannabinoids, melatonin, xenon, argon, allopurinol, and topiramate. These medications are hypothesized to decreased glutamate toxicity, NMDA inhibition, enhancement of gamma-aminobutyric acid, and decreased oxidative stress. Melatonin also plays a role in glial development and a randomized controlled pilot trial is ongoing. Argon is less expensive than xenon and may augment the therapeutic effect of hypothermia.\(^\text{10}\)

Monosialoganglioside is being investigated for its role in maintaining cell membrane integrity,\(^\text{39}\) because ganglioside levels were shown to be reduced in a rat model of neonatal hypoxic ischemic injury.\(^\text{49}\) One meta-analysis that included 787 neonates showed possible benefit, although there is limited information on optimal dosing, safety, and long-term outcomes.\(^\text{50}\)

Creatine has been shown to be neuroprotective in animals, but no randomized controlled human trials have been completed.\(^\text{51}\) The mechanism of action for creatine is not completely understood, but may be related to the inhibition of the caspase-induced cell death cascade associated with cerebral ischemia. Induced focal ischemia in mice fed with a 2% creatine-rich diet and then exposed to a middle cerebral artery occlusion–mediated injury for 4 weeks were noted to have improved neurologic and behavioral scores 24 hours after reperfusion.\(^\text{52}\)

**NONPHARMACEUTICAL INTERVENTIONS**

Delayed cord clamping of 30 seconds or greater is recommended in preterm infants to increase circulating red blood cell numbers in the neonate. Studies have confirmed its safety, observing decreased delivery room intubation and metabolic acidosis at birth, with less respiratory distress syndrome. Delayed cord clamping was also associated with reduced early blood transfusions and intraventricular hemorrhage.\(^\text{53,54}\) It is
theorized that delayed cord clamping may act by increasing the oxygen carrying capacity and thereby increasing neonatal brain oxygenation.

Another investigative therapy used for neuroprotection in term and late preterm neonates is therapeutic hypothermia. This therapy should be started within 6 hours of birth and continued for 72 hours. This therapy is only available in some tertiary care centers and is likely not a viable solution in smaller remote community centers. One small study with 31 preterm neonates (34–35 weeks’ gestation) showed that therapeutic hypothermia is feasible in this population but is associated with increased rates of complications, including significant differences in hyperglycemia (58.1% vs 31.3%, \( P = .03 \)) and early rewarming (19.4% vs 0%, \( P = .009 \)) compared with 32 term neonates.\(^5\)

Another proposed intervention is remote ischemic preconditioning, which is performed by inducing sublethal ischemia to peripheral tissue remote from the area of damage to induce endogenous repair within the central nervous system. This technique is currently being studied in rat models in which the ischemia is induced in the extremities in order to enhance central endogenous repair. Mediators for this response are thought to include phosphorylation, nitric oxide, transporter regulation, inflammatory response, increased glucose metabolism, and angiogenesis.\(^5\)

EXPERIMENTAL PREDICTORS

**Biomarkers**

Another field of active research interest is in the identification of biomarkers to predict the likelihood of developing CP. If found to be accurate and reliable, this has the potential to significantly change clinical management. At present, there are no specific marketed biomarkers that are useful in the diagnosis or prediction of CP. Different markers being investigated include S100B (a calcium binding marker that is released by damaged neurons), neuron-specific enolase (released after neuronal death), glial fibrillary acidic protein (released by damaged astroglia), total tau proteins, and ubiquitin carboxyl terminal hydrolase. Inflammatory markers are also being investigated for their ability to predict or diagnose CP, including interleukin (IL)-6, IL-16, IL-8, and vascular endothelial growth factor. Metabolites such as arachidonic acid, butanoic acid, citric acid, lactate, fumaric acid, malate, propanoic acid, and succinic acid are also being considered.\(^1\)

**Imaging**

Magnetic resonance (MR) spectroscopy is being used to help predict neonatal brain damage but should be performed within 6 hours of delivery in order to be helpful in predicting CP. MR spectroscopy estimates levels of phosphocreatine, inorganic phosphate, or lactate within the brain tissue with levels of phosphocreatine considered protective, whereas high inorganic phosphate and lactate levels are associated with harm.\(^1\) The Magnetic Resonance Biomarkers in Neonatal Encephalopathy (MARBLE) study across 8 neonatal intensive care units in the United States and United Kingdom showed that thalamic proton MR spectroscopy of N-acetyl aspartate concentrations acquired within 14 days of birth in neonates between 36 and 43 weeks’ gestation who also received therapeutic hypothermia provided the single best prognostic indicator of CP at 23 months of age.\(^5\)

**Discussion**

Delivery before 32 weeks’ gestation is responsible for approximately one-third of all new cases of CP.\(^3\) The enormous economic and societal costs associated with CP
underscores the need for primary and secondary neuroprotection measures. Although this article reviews several promising therapies that are under clinical or preclinical investigation, delayed umbilical cord clamping and antepartum MgSO4 administration are the only interventions shown to be effective at this time. These neuroprotective strategies, in conjunction with antenatal corticosteroid therapy for fetal lung maturity and tocolysis to optimize completion of steroid therapy, are the only effective interventions currently available to decrease the morbidity associated with preterm delivery. The absence of a clear consensus regarding MgSO4 dosing for neuroprotection remains a barrier to widespread implementation. Our recommendation is based on the current status of the literature, clinical experience, and existing research. Further head-to-head comparison trials are needed to determine the best dosing and duration of magnesium therapy in order to provide neuroprotection and prevent CP.

REFERENCES


Kind regards
Dr. Love Kumar Shah
Sharins is caring, caring is learning
www.lovekumarsah.com.np