Neuroprotective ability of magnesium sulfate in preterm infants

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Dedication

I would like to thank my family for standing by me since day one and encouraging me to follow my dreams. They have lifted me up during the difficult times and celebrated with me during the exciting times. Mom, Dad, Jill, Kurt, my husband, Bob, and Grandma and Grandpa, I don’t know what I would do without you in my life. You all have stood by me through the good and the bad. I know I can count on you to always be there for whatever life has planned next. Thank you for all you’ve sacrificed and given unselfishly. I love you all more than words could ever express.
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Introduction

Anecdote: Dustin, or “Dusty” as his family calls him, is a 24 year old from Toledo, Ohio who was diagnosed with having cerebral palsy at 3 months of age. His mother, Monica, describes her third pregnancy as “just not feeling right throughout”. Her OB/GYN assured her that everything was checking out fine despite slightly elevated high blood pressure she developed during the pregnancy. No treatment was initiated for the blood pressure. One week after her scheduled due date, Monica experienced a sharp pain in her abdomen which was followed soon after by “a gush of blood”. Her membranes had ruptured. Monica was rushed to the hospital to deliver. Dustin was born unresponsive and not breathing. There was no telling how long his brain had been without oxygen.

The neonatal team at the hospital was able to revive Dustin, but he had to spend several days in the NICU under observation with strict medical care. Slowly he gained enough strength to go home, but only time would tell what sort of long-term damage had been caused. When Dustin is asked about his birth, he tells the same story to everyone. He explains that when he was born, God gave him 3 hours to decide if he wanted to live, having cerebral palsy for life, or die. Dustin chose to live. By 3 months of age, Dustin had developed muscle contractures and seizures. Further tests on his brain and muscle tone led to a diagnosis of spastic quadriplegia cerebral palsy. Today Dustin is a vibrant man full of life who always wears a smile on his face. He is able to read, write, and maneuver around independently in his motorized wheelchair. Although not able to speak many words, a talking machine allows Dustin to type what he wants to say and then it speaks it for him. Both of his parents spend enough time with them that they are able to understand him completely by his looks and gestures alone. He enjoys watching
ultimate fighting, WWE wrestling, and Pittsburgh Steelers’ football. He also likes playing video games and wants to become a doctor someday. His biggest frustration about his cerebral palsy is the way other people treat him. Many think that he is mentally retarded and speak to him as if he cannot understand what they are saying. Some also treat him poorly not realizing he recognizes everything that is going on. Intellectually Dustin is very bright, but some people just see his outside physical disabilities. One of the struggles Dustin deals with is not having friends. Others with disabilities are often too severely handicapped to establish friendships and those that are not disabled typically do not have the patience to spend time with him. Dustin’s mother and father recognize all too well the time requirements necessary to care for a son who is almost completely physically handicapped. The 24/7 needs Dustin has leaves little time for themselves, friends or other family. However, his parents wouldn’t have it any other way. They both agree that the smile on his face each morning is well worth the sacrifices. Monica describes knowing when God is with her son because he gets a particular smile she has come to recognize. She’ll then ask Dustin if God is with him right now and he’ll gently nod his head “yes”.

Preterm birth (occurring before 37 weeks gestation) is a serious health concern for those infants affected. Seventy-five percent of perinatal mortality and more than half the long-term perinatal and infant morbidity are associated with preterm birth. Steady increases in rates of preterm delivery in the United States have been seen over the past 20 years with current rates at 12-13% (1 in 8), up from 9.5% in 1981. Although the precise mechanism of preterm labor is heterogeneous and not known in most cases, theories exist which may explain compounding risk factors which include infection,
inflammation, uteroplacental ischemia, or stress. The ability to know the specific gestational age of the fetus is not an exact science and therefore complicates preterm predictability as well. Initiating causes of preterm birth are subdivided into three groups: 1) indicated for maternal or fetal safety 2) spontaneous with intact membranes 3) preterm premature rupture of membranes (PPROM). (Goldenberg, Culhane, Iams, & Romero, 2008) There are specific circumstances when preterm birth could be considered a safer alternative if the mother or baby are at risk of death or severe injury if delivery does not occur. Some of these conditions include preeclampsia, intrauterine growth restriction, infection, and placental abruption (peeling away of the placenta from the uterus before delivery). Preeclampsia is a condition of pregnancy marked by high blood pressure and excess protein in the urine after 20 weeks of pregnancy. This condition could progress into eclampsia and cause seizures and organ damage (kidney, liver, brain, heart and eye) in the mother. Preeclampsia and some other causes of indicated preterm birth such as placental abruption and intrauterine growth restriction can produce a condition known as ischemic placental disease. This condition disrupts the blood supply to the baby leaving it chronically hypoxic and without nutrition. Preterm delivery in these situations may provide more beneficial outcomes than waiting to deliver full term. (Ananth, et al., 2007) Of initiating factors of preterm birth in general, spontaneous causes (including both spontaneous with intact membranes and PPROM) during 34-36 weeks gestation are by far the most common. PPROM is defined as a spontaneous rupture of the membranes holding the amniotic fluid at less than 37 weeks gestation at least one hour prior to the onset of contractions. Spontaneous preterm births account for more than 2/3 of all preterm births in the United States, whereas
indicated preterm births account for the remainder. (Macones, 2005) Risk factor characteristics for preterm birth have been identified in both the maternal and fetal populations which may make them more susceptible. Mothers who are carrying multiples, are underweight/overweight, use tobacco/drugs, have abnormalities with their uterus or cervix, conceived within six months of a previous pregnancy, have chronic conditions such as hypertension or diabetes, and had a previous preterm birth are all at an increased risk. However, only about half the women who have preterm labor fall into any known risk group. ("Preterm Labor," 2008) It is thought that women who have pregnancies in close proximity to each other may not allow adequate time for the uterus to return to its normal non-inflammatory state, thus causing an increased risk for preterm birth. Another hypothesis is that the previous pregnancy may leave the mother's body in a state of deficiency and a short interval between pregnancies does not leave enough time to replenish stores of essential vitamins and minerals for the next fetus. Identification of at-risk women is an important aspect of optimal care as it allows for initiation of risk-specific treatment including progesterone injections, limitation of activity, and chronic disease management. Although many preterm babies survive due in part to technologic advances that have been made in medicine in recent years, they are still at an increased risk of neurodevelopmental impairments and respiratory and gastrointestinal complications. (Goldenberg, et al., 2008)

**Cerebral palsy overview**

One neurodevelopmental disorder that preterm infants are particularly susceptible to is cerebral palsy, a condition affecting muscle movement, balance and posture due to abnormalities in the brain. Diagnosis of this disorder most commonly
occurs within the first few years of life when symptoms, which include inability or
difficulty crawling or walking, begin to present themselves. However, the diagnosis of
cerebral palsy can be difficult due to the array of presentations seen under this elusive
definition describing nonprogressive brain lesions. These lesions develop before the
age of 3 years and cause activity limitations. Unlike other neurological disorders,
cerebral palsy does not get worse over time, but can be accompanied by other
disorders such as mental retardation (30-50%), seizures (15-60%) and learning
disabilities. Cerebral palsy is caused by damage to the motor control centers of the
young developing brain and can occur during pregnancy (~75%), during childbirth
(~5%) or after birth (~15%) up to about age three while the baby’s brain is still
developing. (Zeldin, Rantanawongsa, & Bazzano) Clinicians typically diagnose
cerebral palsy by evaluating the child’s muscle movements and tone. Children will
usually exhibit some variety of muscular ataxia, lack of muscle control when performing
voluntary movement, or spasticity, stiff muscles and exaggerated reflexes. These
muscular disabilities may first be noticed when the child starts to become mobile and
present with a dragging leg or a limb that appears floppy or stiff. Children under the age
of 12 months usually have not developed hand sidedness, but those with cerebral palsy
may have developed hand sidedness at this point since their affected side may not
allow them its use. The persistence of primitive reflexes can also be used to aid in
diagnosing cerebral palsy. Primitive reflexes, such as Babinski, Moro (startle reflex),
asymmetric tonic neck reflexes (i.e. fencing posture with neck turned in same direction
when one arm extended and other flexed) and suckling, should disappear by this age,
but their persistence can indicate a neurological disorder such as cerebral palsy.
Because the majority of cerebral palsy cases can be diagnosed based on history and physical exam alone, further diagnostic testing is typically not required. However, MRI can be used when the etiology of the patient’s cerebral palsy has yet to be identified or to diagnose other causes of the observed symptoms. The task of diagnosis can be a challenging one though as two patients with cerebral palsy can look very different from one another depending on the severity of the disease. Some children may experience mild symptoms of the disease only affecting a unilateral limb where others can develop severe cases which leave them completely uncommunicative and wheelchair bound. Although many risk factors have been implicated as causes of the development of cerebral palsy including infections (e.g. rubella, cytomegalovirus, toxoplasmosis, and meningitis), insufficient oxygen (e.g. asphyxia or near drowning), severe jaundice, head injury and genetics, preterm birth alone seems to be one of the more powerful ones. The type of cerebral palsy that presents is often identified based on the location of the brain lesion and also according to resting tone and limb involvement (hemiplegia, diplegia, or quadriplegia). The most common type of cerebral palsy is spastic, accounting for 80% of those diagnosed, and related to lesions involving the cortex/pyramidal tracts. This type is characterized by spasticity (increased tone with increased velocity of movement), hyperreflexia, clonus, and an upward Babinski reflex. The second most common type is dyskinetic, or extrapyramidal, which is characterized by abnormal involuntary movements and hypertonicity. (Zeldin, et al.) Children diagnosed with cerebral palsy often develop joint contractures from the sustained muscle contractions and from an inability to stand since standing provides the stresses necessary to form proper skeletal structure. The bones become thin, frail and often
deformed leading to further mobility complications. Speech and language disorders are common in people with cerebral palsy as well. The incidence of dysarthria is estimated to range from 31% to 88% and can involve difficulty swallowing, breathing, and laryngeal dysfunction in addition. Although mental retardation can coexist with cerebral palsy at relatively high percentages, language barriers may mask the true intellectual ability of the child. For this reason, it is very important to assess the child’s learning ability and adapt learning styles as necessary to maximize education potential of the affected child. Approximately 40% of all cerebral palsy patients also have some abnormality of vision. Loss of coordination of the muscles controlling eye movements is very common. The child cannot fix gaze on an object. In half of the cases, binocular vision does not develop. ("Cerebral Palsy Symptoms: Cerebral Palsy Guide for Parents,")

Unfortunately there is no cure for cerebral palsy. Most current treatment is focused on therapy to improve muscle spasticity and movement ability, the primary deficiencies of this disease. Surgery is also an alternative option to loosen tight muscles or correct bone abnormalities for those patients refractive to conservative treatment with braces or orthopedic devices. Treatment is usually symptomatic only for these patients and focuses on helping the person develop as many motor skills as possible or learn how to compensate for the lack of them. (Zeldin, et al.)

As technologic advances in medicine are made, declines in very low birth weight (VLBW) infant mortality are seen, however, coinciding with this decline are increasing rates of cerebral palsy among surviving infants (Vincer, et al., 2006). One recent study conducted involving three regions in the United States (Alabama, Georgia, and Wisconsin) estimates the prevalence of cerebral palsy to be 3.6 cases per 1000, higher
than most previous studies which reported rates between 1.5-3 cases per 1000 (Yeargin-Allsopp, et al., 2008). Extremely premature infants have underdeveloped brains that are particularly susceptible to outside influences contributing to higher incidence of cerebral palsy among this group. A study published in September 2010 from Norway, however, also found an increased risk, yet still extremely small, among post term infants as well. 1,682,441 single births between gestational ages of 37 and 44 weeks with no birth defects were examined from 1967 to 2001. Babies born at 37 weeks had about a 90% increased risk for cerebral palsy, compared to babies born at term (40 weeks). Babies born at 38 weeks had a 30% increased risk, 42 weeks had about a 36% increased risk, and about 44% increased risk for those born after 42 weeks. (Moster, Wilcox, Vollset, Markestad, & Lie, 2010) The severity of cerebral palsy varies greatly and the burden to its victims in severe cases is substantial. Parents of these children are depended upon to provide lifelong supervision and assistance. Such a major time commitment can cause trouble for a family including lost employment opportunities, neglected siblings, and social isolation. Children affected with cerebral palsy can also develop deprivation handicaps. The child who cannot move is deprived of peer interaction and stimulation through play. Having a least one good friend can decrease the feelings of loneliness and promote proper social interaction. Employment opportunities for adults with cerebral palsy have improved in recent years due to specialized training and education programs. (Nelson) A considerable financial burden also exists for families affected by this disorder. The CDC estimated the lifetime cost in 2003 dollars for those children born in 2000 with cerebral palsy to be $11.5 billion or $921,000 per person. These estimates reach the heights they do because the majority
of children with developmental disabilities require long-term supportive care and services. (Honeycutt, et al., 2004) As evidenced by these numbers, action to prevent developmental disorders is critically important. Recent studies have attempted to uncover a new indication for magnesium sulfate by demonstrating its potential to prevent the development of cerebral palsy in those preterm infants to whom it was administered. Magnesium sulfate has shown the ability to provide neuroprotection to the fetal brain by counteracting damaging processes thought to be causes of cerebral palsy or other similar developmental disorders producing lifelong disabling affects.

**What is magnesium sulfate?**

Magnesium is an important element in the body that is used for enzymatic reactions and plays an important role in neurochemical transmission and muscular excitability. It is also necessary for proper function of potassium and calcium channels, helping to regulate action potentials in cardiac and neural tissues. This particular element, however, has to remain closely balanced as deficiencies and excesses can cause serious complications (normal plasma magnesium levels range from 1.5-2.5 mEq/L). Those who develop magnesium deficiencies (< 1.5 mEq/L in serum) will typically present with neuromuscular irritability, CNS hyperexcitability and cardiac arrhythmias which may include any of the following: hyperactive deep tendon reflexes, muscle cramps/twitches, tremors, irritability, psychosis, ataxia, paroxysmal atrial and ventricular dysrhythmias, and weakness. Excesses of magnesium (> 4 mEq/L) can also cause serious problems including death. The first sign of excess magnesium is decreased deep tendon reflexes which will disappear all together as levels approach 10 mEq/L. Heart block may also occur at this level and eventually progress to respiratory
depression if levels continue to rise. Magnesium sulfate is a commonly administered medication in the United States used most often in women during labor and delivery either as a tocolytic (a medication that can inhibit labor, slow down or halt the contractions of the uterus) or for seizure prophylaxis in women with preeclampsia. If left untreated, preeclampsia can progress to the point of seizure development, at this point called eclampsia. Magnesium sulfate is considered first-line therapy in patients with preeclampsia and eclampsia. It works to prevent or control seizures by decreasing the amount of acetylcholine released at the motor end plate by the nerve impulse. Acetylcholine is necessary for muscle contraction therefore impeding its release at the end plate blocks neuromuscular transmission. When this drug is chosen as a treatment option, levels must be monitored closely as its side-effects can be somewhat unpleasant. The most common side-effects of this drug are flushing, diaphoresis, hypotension due to its vasodilating potential, depressed cardiac function, electrolyte imbalance and drowsiness. It should also be used with caution in those taking other CNS depressants (such as barbiturates, narcotic, or hypnotics) as the effects can be synergistic. In severe preeclampsia or eclampsia, a total initial dose of 10-14g of magnesium sulfate is given. This dose is typically given by infusing 4g intravenously along with 4-5g intramuscularly into each buttock. The 4-5g IM injections are then continued every 4 hours until convulsions cease while monitoring for the continuing presence of the patellar reflex and adequate respiratory function (>12 respirations/minute). Alternatively, after the initial IV dose, some clinicians administer 1-3 g/hour by constant IV infusion in place of the IM injections for instances where therapeutic levels are desired immediately as in eclampsia. A serum magnesium level
of 6g/100mL (3.0-7.5 mEq/L) is usually sufficient for control of seizures. Deep tendon reflexes begin to diminish when magnesium levels exceed 4 mEq/L therefore patellar reflexes should be assessed before each additional administration. Absence of these reflexes indicates magnesium should be held until their return. A total daily (24 hr) dose of 30-40 g should not be exceeded. ("Magnesium Sulfate," 2010) Tocolysis treatment carries its own set of standards separate from preeclampsia therapy. The main goal of tocolytic therapy is to delay labor at least 48 hours to allow administered corticosteroids to help develop the immature fetal lungs. A variety of tocolytic agents exist which include calcium channel blockers (nifedipine), betamimetic drugs (terbutaline), prostaglandin synthetase inhibitors, NSAIDS and magnesium sulfate. Tocolysis should only be considered if the cervix is < 4cm dilated, amniotic sac is intact, and fetus is not in distress. Although magnesium sulfate has been used by obstetricians for many years to obtain tocolysis, recent trials are questioning its effectiveness and safety compared to other treatment options. Tocolytic dosages of magnesium sulfate begin with 4-6g IV over 20 minutes followed by 2-4g/hr as a continuous infusion for the next 12-24 hours until contractions cease. (Briggs & Wan, 2006) At these infusing rates over a 24 hour period as much as 50g or more of magnesium sulfate can be given to the patient increasing the likelihood of adverse reactions. Monitoring of the mother and fetus every 30-60 minutes while infusing the magnesium is therefore necessary (blood pressure, respirations, and deep tendon reflexes). Recent studies suggest that neither magnesium sulfate nor any of the other tocolytics show much benefit in stopping labor. Because magnesium sulfate specifically is considered to be ineffective as a tocolytic, potentially harmful to infants, and unpleasant for women, other tocolytics should be
considered and/or tried first. (Grimes & Nanda, 2006) A Cochrane review of the world’s randomized controlled trials comparing magnesium sulfate to other accepted tocolytics found that magnesium sulfate has no clinical benefit. A more appropriate first-line choice for a tocolytic would be a calcium channel blocker due to its higher rate of effectiveness, decreased adverse reactions, and decreased adverse fetal outcomes compared to other tocolytic agents. Therefore, magnesium sulfate should only be used as a tocolytic if other agents have already been tried and failed. (C. Crowther, Hiller, & Doyle, 2002) Studies conducted on women administered magnesium sulfate for both tocolysis and preeclampsia over the past 10-15 years have shown intriguing data related to lower incidence of cerebral palsy among exposed infants prompting further analysis of this finding. Although the exact mechanism by which magnesium sulfate works to protect the infant brain from damage is yet to be determined, a few theories based on animal models exist to explain the findings. A connection between its known mechanism as a tocolytic via blockage of the voltage-gated calcium channels required for muscle contraction may exist as well. Infants diagnosed with cerebral palsy very often have periventricular white matter injury, a pathologic lesion resulting from damage to susceptible immature preoligodendrocytes before 32 weeks gestation. This type of brain cell provides support to axons and produces the myelin sheath. The myelin sheath is a vital component to nerve development as it is necessary for nerve impulse conduction and proper signaling. Periventricular white matter injury is thought to be due to ischemia-induced oxidative stress and excitotoxicity resulting from extreme stimulation of glutamate receptors on these precursor cells. More recent studies have specifically suggested N-methyl-D-aspartate (NMDA) glutamatergic receptor (a
predominant excitatory neurotransmitter pathway) overstimulation could be involved in preoligodendrocyte injury. As research in this area produces better understanding, evidence now suggests that blocking NMDA receptors to glutamate can provide significant neuroprotection to the fetal brain. (Conde-Agudelo & Romero, 2009) Magnesium could prevent this overstimulation by acting as a calcium antagonist at these receptors in the brain. This suspected mechanism would be similar to how magnesium sulfate works in the uterus to inhibit contractions when given for tocolysis by preventing calcium influx into the cells. Magnesium sulfate has been shown in animal models to have the ability to antagonize NMDA regulated receptor activity thus reducing neuronal cell death and damage related to increased intracellular calcium (Figure 1). Knowledge that magnesium deficiency causes decreases in antioxidant defenses and cell death also support this theory. (Mercer & Merlino, 2009) Another, less evidence supported, theory also exists suggesting that magnesium sulfate may limit the action or prevent the entrance of inflammatory cytokines into the brain. This idea is based on data from animal models linking magnesium sulfate deficiency to exaggerated inflammatory cytokine response and altered immune function. Because the inflammatory response could actually be the cause of cerebral lesion development, blocking the activation or production of these harmful cytokines could limit the amount of damage to the vulnerable infant brain. (Blackwell, et al., 2001)

Even though the exact mechanism by which magnesium sulfate may provide neuroprotection is not known specifically, the correlation has produced many questions and inquiries. The purpose of this clinical review is to examine studies that analyzed the correlation between administration of magnesium sulfate to mothers in preterm
labor and the prevalence of development of fetal neurological brain damage, specifically cerebral palsy. Further knowledge of the efficacy of magnesium sulfate to prevent fetal brain damage, beneficial differences amongst gestational age groups, and appropriate dosages needed to be most effective without causing unnecessary harm is essential to understand this theory entirely.
Methods

Multiple databases (including PubMed, Google Scholar and Medline) were searched using a combination of key words that included but are not limited to: cerebral palsy, neuroprotection, magnesium sulfate, preterm labor, and white matter injury. Trial preference was given to those conducted within the last ten years and done in a randomized controlled approach. All trials included in this review involved the administration of magnesium sulfate to mothers in preterm labor near delivery with a placebo being given to approximately half of the participants. The trials also contained some sort of neurodevelopmental component in order to assess the severity and/or existence of cerebral palsy in those infants enrolled.
Findings

Several studies exist, including 3 randomized controlled trials, which examine groups of pregnant women exposed to magnesium sulfate preterm and rates of cerebral palsy within those groups compared to unexposed women delivering preterm. A closer look at each of these trials is necessary to determine similarities and differences amongst the groups and the findings.

The Australasian Collaborative Trial of Magnesium Sulfate (ACTOMgSO4)

This randomized controlled trial conducted by Crowther et al. enrolled 1062 pregnant women from 16 different hospitals in Australia and New Zealand. Women were eligible for the trial if they were pregnant with single, twin, triplet, or quadruplet fetuses younger than 30 weeks’ gestational age and if birth was planned or expected within 24 hours. Exclusion criteria included those in the second stage of labor, previously administered magnesium sulfate during current pregnancy, and contraindications to receiving magnesium sulfate (low maternal respiratory rate, absent reflexes, decreased urine output/renal failure, and hypocalcemia). Randomization numbers were generated by computer and each eligible consenting participant was given a treatment pack. Each treatment pack looked identical and contained and infusion bag of 60 mL of either 0.5 g/mL of magnesium sulfate or isotonic sodium chloride solution. Women were given a loading dose of 8 mL (4g) for 20 minutes by a maintenance infusion of 2 mL/h until birth or up to 24 hours. Blinding was maintained throughout the entire trial. Surviving infants had an ultrasound performed within the first few days of life to detect intraventricular hemorrhage (IVH) or periventricular leukomalacia, pathologic lesions often discovered in the brains of infants who go on to develop cerebral palsy. The children were then
evaluated at a corrected age of 2 years by blinded developmental pediatricians and psychologists to assess signs of cerebral palsy and/or developmental severity. The evaluators were not trained specifically in cerebral palsy diagnosis, but were asked to evaluate the child’s gross motor function, vision, hearing, and a psychological assessment (neurosensory outcomes) using identified criteria and indices. Both the control and experimental groups were similar in mean maternal age (magnesium sulfate = 28.4 years old, control = 28.7 years old) and median gestational age at entry (magnesium sulfate = 27 weeks 3 days, control = 27 weeks 2 days) with a range between 25 weeks 5 days to 28 weeks 5 days for both groups. Reason for preterm birth was also comparable between the groups with the overwhelming majority being caused due to preterm labor (62%). The exposed women received a loading dose of magnesium sulfate followed by a maintenance infusion totaling on average 13mL (9-28mL). Results of the study revealed the magnesium sulfate group to have lower primary outcome rates of total pediatric mortality, cerebral palsy, and the combined outcome of mortality or cerebral palsy, although the data collected did not reveal a statistically significant difference. Secondary outcomes before hospital discharge and at a corrected age of 2 were also evaluated. Infants were assessed for IVH, periventricular leukomalacia, chronic lung disease, and mechanical ventilation before being discharged and no significant difference between the two groups was shown. Neurosensory outcomes were then assessed at age 2 which revealed no overall significant differences. Lower rates, however, were once again noted in the magnesium sulfate group in regards to severity of cerebral palsy (magnesium= 12 moderate, 3 severe; control= 15 moderate, 6 severe) and gross motor dysfunction (magnesium= 18
substantial; control= 34 substantial). A statistically significant difference was noted in the magnesium sulfate group upon further neuromsensory analysis when comparing substantial gross motor dysfunction (not walking independently) and combined outcome of death or substantial gross motor dysfunction between groups. Higher maternal adverse side effects were noted in the magnesium sulfate group as expected, but none were serious or life threatening. (C. A. Crowther, Hiller, Doyle, Haslam, & Australasian Collaborative Trial of Magnesium Sulphate Collaborative, 2003)

**PREMAG Trial**

Another randomized controlled trial conducted in multiple centers in France enrolled 573 pregnant women with single, twin, or triplet fetuses less than 33 weeks of gestational age if birth was expected or planned within 24 hours. No lower limit gestational age was established. Exclusion criteria included fetal chromosomal abnormalities, fetal hypotension, administration of other tocolytic within the last 24 hours, signs of cardiovascular toxicity, renal insufficiency, pregnancy-related vascular disease (e.g. preeclampsia, growth restriction), indication for emergency caesarean section, or administration of betamimetics, aminoglycosides, or steroids for at least 1 hour prior to treatment. Randomization numbers were generated by computer and each eligible participant was given a treatment pack via a centralized coordinating pharmacy. Each treatment pack was identical and contained either 0.1 g/mL MgSO4 or isotonic 0.9% saline. Participating women were given either 4.0g of magnesium sulfate or saline via infusion over 30 minutes. Both the control and experimental groups were similar in median gestational age at entry (30 weeks) with a range between 24 weeks to 32 weeks 6 days for the magnesium sulfate group and 23 weeks 4 days to 32 weeks 6
days for the control group. Mean maternal age was also similar between groups (magnesium sulfate = 29.3 ± 5.3, control = 29.5 ± 5.1). The designers of this study classified it as a single blind study as the anesthetists were made aware of the assigned treatment to be able to take any immediate action needed against adverse side effects of the magnesium sulfate. They also thought the obstetricians were able to identify the groups based on observed side effects alone, such as flushing. Both groups also had similar reasons for preterm birth with preterm labor and PPROM as the top causes respectively. The majority of participants in each group also received antibiotics, corticosteroids, and tocolytics. Maternal and fetal outcomes at birth were similar between groups including interval from infusion to delivery and placental weight. The only significant difference noted in characteristics at birth was the higher rate of maternal-fetal infection in the magnesium sulfate group. Differences were also seen in the magnesium sulfate group that approached significance which included an Apgar score of <7 and apnea/bradycardia. The primary outcomes in this trial included examination of neonatal mortality before discharge, severe neonatal white matter injury (WMI), and combined severe WMI and/or mortality. WMI, acquired damage to areas of white matter within the brain, is incriminated as the source for neurodevelopmental disorders including cerebral palsy. No statistically significant difference was found for primary outcomes between the two groups, although minimally lower rates were seen across the board in the magnesium group. There were also minimally lower rates of all WMI (severe or not) and infant nonparenchymal/intraparenchymal brain hemorrhages seen in this group, but once again did not reach significance. Similar maternal and fetal
adverse outcomes were seen for both the experimental and placebo groups. (Marret, et al., 2006)

**BEAM Trial**

The third randomized controlled trial conducted in centers across the United States enrolled 2241 women at an average age of 26 years carrying singletons or twins between 24 and 31 weeks gestation. Women were eligible if they were considered at a high risk for spontaneous delivery due to rupture of membranes, in advanced preterm labor with dilatation of 4 to 8 cm and intact membranes or indicated preterm delivery was anticipated within 2 to 24 hours (e.g. fetal growth restriction). Exclusion criteria included anticipated delivery within less than 2 hours, cervical dilatation >8cm, ruptured membranes <22 weeks, major fetal abnormalities, maternal hypertension or preeclampsia, and receipt of IV magnesium sulfate within the past 12 hours.

Randomization was computer generated in a double blind fashion. Participating women were given a loading dose of 6 grams of either the magnesium sulfate or identical appearing placebo infused over 20-30 minutes followed by a maintenance infusion of 2 grams per hour. The infusion was discontinued if delivery had not occurred within 12 hours or no longer seemed imminent. The median total dose of the study drug received by women in the magnesium sulfate group was 31.5 g (interquartile range, 29.0 to 44.6). Both groups had virtually identical mean gestational ages at the time of randomization (28.3 weeks ± 2.5). Infants were evaluated by a certified pediatrician or pediatric neurologist at 2 years of age to determine if a diagnosis of cerebral palsy was appropriate. A diagnosis of cerebral palsy was made if two or more of the following three features were present: a delay of 30% or more in gross motor developmental
milestones (inability to sit or walk by appropriate age); abnormality in muscle tone, markedly decreased/absent deep tendon reflexes, or movement abnormality (posturing or gait asymmetry); or presence of primitive reflexes or absence of protective reflexes. If cerebral palsy was diagnosed, severity was then assessed using a gross motor function scale. Although this study did not find a significant difference with regards to magnesium sulfate treatment for the primary outcome of moderate/severe cerebral palsy at 2 years of corrected age or stillborn/infant death by 1 year of corrected age, differences were seen upon closer examination. A significant difference was identified in the magnesium sulfate group when looking at moderate/severe cerebral palsy (unable to walk independently or grasp a block with both hands) alone. Lower rates were noted most specifically in pregnancies less than 28 weeks. 6.0% of those at a gestational age less than 28 weeks that received the placebo developed moderate to severe cerebral palsy, whereas only 2.7% of those that received magnesium sulfate did. A questionable slight increase was seen regarding the incidence of fetal or infant death with magnesium sulfate administration for all gestational ages. This was partially corrected by eliminating those children with major congenital anomalies. Adverse reactions were expectedly higher in the magnesium sulfate group, however, no serious or life threatening events occurred. (Rouse, et al., 2008)

Magpie Trial
This randomized controlled trial initially did not look at magnesium sulfate’s effect on neurodevelopmental disorders specifically. Instead, this experiment was conducted originally to examine the effects of magnesium sulfate on women with preeclampsia and their babies compared to other anticonvulsant therapy or placebo. This widely diverse
study included 125 centers in 19 countries in its data collection, analyzing a total of 10,141 women. Women were eligible to participate if they had preeclampsia and there was uncertainty whether to use magnesium sulfate. They also were required to have not yet given birth or be <24 hours postpartum, blood pressure >140/90 mm Hg on two occasions and proteinuria 1+ or more. Exclusion criteria included hypersensitivity to magnesium, hepatic coma with a risk of renal failure, and myasthenia gravis.

Participating women were randomly assigned to receive either magnesium sulfate or placebo. The identical treatment packs dispersed contained a 10 mL ampoule of either 5g magnesium sulfate or 10 mL normal saline, 10 mL calcium gluconate for use in the event of toxicity, and an eclampsia rescue pack. The eclampsia rescue pack contained two ampoules to be used in the event of an eclamptic seizure. The first ampoule contained 5g (10mL) of magnesium sulfate. The second ampoule contained 5g (10mL) of either magnesium sulfate or placebo, whichever was the opposite of the trial allocation. Both of these ampoules were to be administered IV followed by magnesium sulfate maintenance therapy in the event of a seizure. Trial participating women were administered a 4g (8mL) loading dose of magnesium sulfate IV over 10-15 minutes. This was followed by an infusion rate of 1g (2mL) per hour IV or 5g (10mL) every 4 hours IM for 24 hours. Monitoring of the patient continued throughout trial treatment with reflexes and respiration being checked every 30 minutes and urine output every hour. If reflexes were slow, respiration rate depressed or urine output reduced, treatment volume was reduced by half for the next administration. Maternal mean age between the groups was similar at 27 years. The majority of fetuses (74%) in both the magnesium sulfate and control groups were >34 weeks gestation at the time of trial
The median total volume of magnesium sulfate administered was 18g (IQR 9-29g). Follow-up of only those children exposed to magnesium sulfate before birth was conducted at 18 months to determine long-term risk of magnesium sulfate which included assessment neurodevelopmental disorders as well. A total of 4483 children recruited before delivery in the original trial were included in the follow-up study, with data from 3283 children available for analysis. An Ages and Stages Questionnaire (ASQ), designed to assess children’s developmental performance between the ages of 4 to 60 months, was mailed out to selected women from the Magpie Trial. The questionnaire looked specifically at five domains of child development (communication, gross motor, fine motor, problem solving, and personal social) graded by the parent to represent the child’s ability to perform a task. These assessments were then compared to age appropriate levels to determine if a possible disability existed which would warrant further pediatric evaluation. A total of 2610 completed evaluation forms were returned. There was approximately the same number of children contacted from the original study in both the magnesium sulfate and placebo groups that were less than 33 weeks gestational age (preterm) at the time of labor and delivery. Closer examination of the data complied using questionnaires and further physician evaluation if needed to recognize neurosensory disability (blind, deaf, unable to walk independently) and severe cerebral palsy, revealed relatively minor differences between groups. For those treated with magnesium sulfate, only 3 of the responding 1431 children were diagnosed with severe cerebral palsy and 13 with neurosensory disability. On the placebo side, however, there were higher rates of severe cerebral palsy and neurosensory disability with 9 and 19 respectively out of the total 1464 from
this group responding to follow-up. However, this was not a statistically significant
difference. The lack of study participants having a neurodevelopmental disorder is most
likely due to the fact that no cutoff in gestational age existed in the original study design
which looked at preeclampsia specifically. This would have limited inclusion to only
preterm infants, those most susceptible to neurological damage. Limited follow-up in
relation to the total number of participants in the original study may also skew the
detected incidence of neurodevelopmental disorders by leaving out potentially valuable
data. (Magpie Trial Follow-Up Study Collaborative, 2007)
Discussion

Although overwhelming evidence does not currently exist to definitively declare that magnesium sulfate has neuroprotective ability in preterm infants, magnesium sulfate does appear to make a difference in specific areas of development and/or disability. Women at risk of preterm birth who are administered magnesium sulfate seem to have better infant outcomes with decreased rates of cerebral palsy and substantial gross motor dysfunction. (Doyle, Crowther, Middleton, & Marret, 2009) Reviewing all trials individually and comparing results reveals fetuses between 28-32 weeks gestational age most likely benefit the most from the magnesium sulfate exposure. Fetuses <28 weeks may also benefit neurologically from magnesium sulfate, however, it is difficult to assess as many other aspects of fetal development come into play at such an immature stage of development. The lowest gestational age in which magnesium sulfate was administered in the included trials was 24 weeks by the BEAM trial. A conclusive decision about neuroprotective effectiveness at this level of prematurity cannot be made based on this trial alone, however. Fetuses enrolled in the BEAM trial at gestational ages <28 weeks were included in the <30 weeks gestational age group and not placed into a group of their own. An inclusion group of this size with a broad age range makes it difficult to determine exactly which gestational ages are benefitting. It appears from the trials reviewed that fetuses >34 weeks gestational age do not benefit as significantly neurologically as those 28-32 weeks from the preterm magnesium sulfate administration. Reasons for this difference are not quite clear but may be attributable to a different mechanism for the development of cerebral palsy at more mature gestational ages. Evidence from these trials demonstrating differences
among varying maternal demographics (age, parity, race, reason for preterm birth), besides fetal gestational age, was not found.

Magnesium sulfate is a commonly administered medication used to treat preeclampsia due to its availability and low cost. However, this drug has a fairly narrow therapeutic window and even slightly high doses of this medication can cause serious side effects including respiratory depression and hypotension. Therefore, careful monitoring of respiratory rate and deep tendon reflexes is required when administering this drug. Comparing the magnesium sulfate neuroprotective trials, some evidence does seem to exist to support the use of this drug for prophylaxis of fetal brain injury in preterm infants. Three reviews have now been completed comparing all five trials as a whole to determine overall neuroprotective potential of magnesium sulfate. All are in agreement that magnesium sulfate given antenatal to mothers at risk of preterm labor substantially improves their unborn baby’s outcome of developing severe-moderate cerebral palsy and substantial gross motor dysfunction. A Cochrane Review published in 2009 found an absolute risk of developing cerebral palsy to be 3.7% for babies exposed to magnesium sulfate and 5.4% for babies unexposed (a reduction of 1.7%). The reviewers also calculated 63 women would need to be treated for one baby to benefit from the magnesium sulfate therapy. (Doyle, Crowther, Middleton, Marret, & Rouse, 2009) A meta-analysis also published in 2009 reported similar findings noting decreased rates of moderate-severe cerebral palsy and combined death or cerebral palsy. Reviewers of this analysis found a significantly reduced risk of cerebral palsy of any severity and of handicapping cerebral palsy (moderate-severe disease) by 30% and 40-45% respectively with fetal exposure to magnesium sulfate. They also made
mention in their report that no increase in perinatal, infant, or maternal death was found in women given magnesium sulfate. This report calculated 46-56 fetuses would need to be exposed to magnesium sulfate in utero before 30 or 32-34 weeks, respectively, to prevent one case of cerebral palsy. For those studies reporting effects on fetuses <30 and <32-34 weeks gestational age, the magnesium sulfate therapy seemed to be most beneficial at improving overall mortality, moderate-severe cerebral palsy and combined death or moderate-severe cerebral palsy. These results were most significant in the BEAM and ACTOMgSO4 trials. The BEAM trial noted the following relative risk (RR) for trials involving fetuses <30 weeks gestational age: death= 0.58 (CI 95% 0.39-0.85), moderate-severe cerebral palsy= 0.54 (CI 95% 0.3-0.96). Similar RR were also found for those trials enrolling fetuses <32-34 weeks gestational age. The ACTOMgSO4 trial noted the following relative risk (RR) for trials involving fetuses <30 weeks gestational age: moderate-severe cerebral palsy= 0.53 (CI 95% 0.3-0.93), combined death or moderate-severe cerebral palsy= 0.75 (CI 95% 0.6-0.94). Similar RR were also found for those trials enrolling fetuses <32-34 weeks gestational age. A major difference between all five trials, however, is the total dosage of magnesium sulfate given to participants. In the PREMAG and ACTOMgSO4 trials, participants were given relatively low doses of magnesium sulfate totaling no more than 10g (median exposure). The BEAM and Magpie trials administered higher doses reaching 31.5g and 18.0g respectively. (Costantine, Weiner, Eunice Kennedy Shriver National Institute of Child, & Human Development Maternal-Fetal Medicine Units, 2009) A comparison of all four trial dosages can be found in Table 1. A concern of many clinicians when administering high doses of magnesium sulfate at tocolytic levels, as in the BEAM and Magpie trials,
is fetal toxicity. The outcomes between the 4 randomized controlled trials analyzed showed relatively consistent findings. For the outcome of cerebral palsy, there was an inclination toward improved outcomes (development of moderate-severe cerebral palsy) in all treatment groups. Interestingly, the improved outcomes seen in infants exposed to magnesium sulfate were nearly the same or better in the low-dose trials, ACTOMgSO4 and PREMAG, compared to those in the higher-dose trials. A very slight increase in pediatric mortality, although not statistically significant, was noted within some population groups in the high-dose trials. This increase in pediatric mortality was not apparent in the low-dose trials, which in fact showed a decrease in mortality. These findings provide further evidence that high doses of magnesium sulfate may surpass their beneficial potential of neuroprotection and instead cause toxicity. Therefore, lower dosages of magnesium sulfate seem to provide the necessary neuroprotection without incurring undesired toxicity. The evidence gathered from these trials suggests the appropriate total dose of magnesium sulfate to maximize neuroprotection would probably be greater than 4g but no more than 10-12g due to the increased risk of death to the fetus seen with doses exceeding this amount. (Pryde & Mittendorf, 2009)

A problem that exists in trying to prevent neurodevelopmental disorders like cerebral palsy is the multifactorial component of these disease processes. It is extremely difficult to pinpoint the cause of cerebral palsy in most cases (i.e. only a small percentage of those who develop cerebral palsy may have done so via the overstimulation theory antagonized by magnesium sulfate). Therefore, determining the mechanism attributable ahead of time in order to administer the appropriate protective medication is not an easy task. It actually requires more of an educated guess on
behalf of the treating provider to determine potential risk factors for each individual case and how they may correlate to a proposed mechanism. It may prove beneficial in later trials that multiple medications with different neuroprotective mechanisms should be administered to counteract the multiple components leading to the development of cerebral palsy. For example, intrauterine infection is also a known risk factor for the development of cerebral palsy, therefore, co-administration of magnesium sulfate with antibiotics may be something to consider. Other processes may also exist that are not known about yet which may play a part as well. We are also limited in the realm of fetal physiology which tends to be very different in preterm infants compared to full term infants. Although advances in neonatal development have seen much progress over recent years, many unknowns still exist. Undoubtedly much more research is needed in this area, but that does not necessarily mean treatment should not occur based upon uncertainty alone. The trials discussed have provided a strong basis of understanding and have proven differences in the lives of these children can be made. Because magnesium sulfate is a relatively safe drug when administered with care, few serious side effects in the experimental groups were seen. Therefore, although not a totally benign medication, the risks of administering magnesium sulfate to women in preterm labor seem to be less than risking an increase in the development of cerebral palsy. It is important to note, however, that there is no guarantee that giving magnesium sulfate will prevent cerebral palsy. Based on the currently published literature, rates as well as severity were somewhat lower in the experimental groups. As stated previously, because cerebral palsy is a multifactoral condition, no absolute answer exists at the time of delivery; only time will tell.
Conclusion

The data analyzed and reviewed from four randomized controlled trials (ACTOMgSO4, BEAM, PREMAG, and Magpie) and three meta-analyses reveals evidence suggesting that in utero magnesium sulfate exposure in mothers at risk of preterm delivery reduces the risk of neurodevelopmental disease occurrence as well as severity, specifically cerebral palsy. Participating women exposed to magnesium sulfate most commonly experienced minor, expected side effects of the medication (flushing, hypotension and tachycardia). No serious or harmful effects to either mother or fetus were found to be any greater in the magnesium sulfate treatment groups than the placebo groups. Drawing specific conclusions about the published trials is difficult due to the differences in inclusion criteria, treatment regimens, and evaluated outcomes. Provided this evidence on the beneficial role magnesium sulfate plays in reducing cerebral palsy incidence and severity, further studies regarding this finding are still required. Specific dosage and timing of magnesium sulfate administration need to be compared to determine ranges that are most beneficial without causing unnecessary complications or side effects. Drug therapies should only be used and recommended for the majority of a population when clear evidence exists that its benefits exceed the risks. Therefore, a beneficial next step would be to determine a “therapeutic window” for magnesium sulfate to specifically provide neuroprotection. Useful information may also be found in assessing the children enrolled in the studies later in childhood to determine other potential neurological motor and/or cognitive effects not detected at the time of initial evaluation. It will also be necessary to pinpoint specific populations of women that would be of highest beneficial potential in regards to their age, reason for
preterm labor, carrying multiples, gestational age, and obstetric history. Although there are still “holes” and unknowns relating to magnesium sulfate therapy, the evidence as a whole is sufficient to suggest neuroprotective qualities do exist.
References


Bier, E. (2009). *Associative activation of the NMDA type glutamate receptor.*


## Table 1: Comparing the Four Recent Neuroprotective Trials

<table>
<thead>
<tr>
<th>Trial</th>
<th>Magnesium Sulfate (g)</th>
<th>Cerebral Palsy (%)</th>
<th>Death (%)</th>
<th>Death or CP (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACTOMgSO4</td>
<td>&lt; 10.5g*</td>
<td>+1.4</td>
<td>+3.3</td>
<td>+4.2</td>
</tr>
<tr>
<td>PREMAG</td>
<td>4g only</td>
<td>+3.2</td>
<td>+1.6</td>
<td>+4.1</td>
</tr>
<tr>
<td>Magpie</td>
<td>18g*</td>
<td>+0.5</td>
<td>-1.2</td>
<td>-0.9</td>
</tr>
<tr>
<td>BEAM</td>
<td>31.5g*</td>
<td>+1.6†</td>
<td>(-1.0)</td>
<td>+0.4</td>
</tr>
</tbody>
</table>

Positive numbers reflect a beneficial difference; negative numbers reflect a non-beneficial difference.

* Median exposure.
† Statistically significant.
Figures

Figure 1: NMDA Glutamate Receptor

**Associative Activation of the NMDA Type Glutamate Receptor**

(Bier, 2009)
Abstract

Objective: Cerebral palsy is a non-progressive disorder of the brain that affects muscle movement, balance and posture. The purpose of this paper is to examine the use of magnesium sulfate during preterm labor to provide neuroprotection to the infant in order to reduce the incidence of cerebral palsy.

Method: Literature review incorporated multiple online databases including MEDLINE, PubMed, Google Scholar and the Cochrane Library. Search terms included cerebral palsy, neuroprotection, magnesium sulfate, preterm labor, and white matter injury.

Results: Four randomized controlled trials and three meta-analyses were reviewed. Overall rates as well as severity of cerebral palsy were somewhat lower in preterm infants whose mothers had antenatal magnesium sulfate exposure during preterm labor.

Conclusion: Current evidence suggests that in utero magnesium sulfate exposure of fetuses whose mothers are at risk of preterm delivery reduces the incidence and severity of neurodevelopmental disease, specifically cerebral palsy.