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Abstract

Infants born very prematurely have a greatly increased risk of suffering permanent neurologic sequelae such as cerebral palsy (CP), a leading cause of physical disability in childhood (Doyle, Crowther, Middleton, Marrett, and Rouse, 2010; Stanley and Crowther, 2008). The risk of developing CP increases exponentially as gestational age at birth decreases (Ancel, Livinec, Larroque, et al., 2006). Observational studies conducted during the 1980s and 1990s found pre-term infants exposed in utero to magnesium sulfate (MgSo4) had decreased incidence of CP (Cahill, Stout, and Caughey, 2010). This paper compares data from several randomized trials as well as meta-analyses to determine whether a relationship exists between antenatal MgSo4 exposure and decreased incidence of CP.

Defining the Problem

CP is defined by O'Shea (2008, pg 35), as "a disorder in posture and movement due to a defect in or lesion of the immature brain." This disorder results in permanent, non-progressive symptoms ranging from mild tremor to quadriplegia (Hayes, 2010). Sensation of the hands is impaired in about half of all cases and chronic pain is reported by more than 25% of adults. Up to 80% of affected individuals have at least some impairment of speech (Odding, Roebroeck' and Stam, 2006). Low visual acuity is reported in almost 75% of all affected children (Odding et sl., 2006). 50% of all children have gastrointestinal and feeding problems, and stunted growth occurs in 25% (Odding et al., 2006). Significant monetary costs are also associated with CP, both for affected persons, and society in general. A 2004 report by the United States Center for Disease Control and Prevention estimated lifetime costs, including medical, non-medical, and

productivity losses, for CP patients born in the year 2000 to reach 11.5 billion dollars (Honeycut, Dunlap, Chen, al Homsi, Grosse et al., 2003).

Background

CP is the most common cause of physical disability in children (Reddihough and Collins, 2003), affecting approximately 3.6 per 1000 or about 1 in 246 individuals (Yeargin-Allsopp, Doernberg, Benedict, Kirby, and Durkin, 2008). While the prevalence of CP has remained stable for two decades (Hankins and Speer, 2003), Crowther et al. (2010) found the prevalence among very premature infants (born less than 34 weeks gestation), and very low birthweight infants (born weighing less than 1500 grams), is rising. This rise is likely attributable to the a general rise in the rate of pre-term births.

In the United States 12.8% of births occur prematurely in 2006, up 21% from 1990, with infants as young as 23 weeks gestation now commonly surviving the neonatal period (Cahill et al., 2010; Doyle, et al., 2010). This is potentially problematic as the risk of developing CP is inversely related to gestational age at birth, with term infants having 0.1% prevalence (Cahill, et al., 2010) compared to a nearly 20% prevalence in infants born before 26 weeks gestation; a 200 fold increase (Ancel et al., 2006). The correlation between very early birth and increased prevalence of CP is likely due to the over-all immaturity, putting pre-term infants at increased risk of neurologic insult.

Describing a specific etiology of CP is difficult as its origins are often multifactorial or unknown (Lawson and Badawi, 2003; Reddihough and Collins, 2003). Prenatal events are thought to be responsible for approximately 70-75% of all cases of cerebral palsy, although it is

usually impossible to determine the exact nature and/or timing of the damaging event (Reddihough and Collins, 2003). The remaining 25-30 % of CP cases are thought to result from an insult to the brain during birth or the neonatal period resulting in a permanent change in brain structure or function (O'Shea, 2008). Neonatal events known to increase the risk of neurologic injury and CP include intracranial bleeding, hypoxic ischemic injury, septicemia, multiple gestation and others (Reddihough and Collins, 2003).

Like the etiology of CP, the exact mechanism of MgSo4 in providing neuroprotection remains unknown and may be multi-faceted. There is, however, evidence in animal studies that MgSo4 may augment secondary effects of neurologic injury. Research by Perlman (2006) found hypoxic brain injury to cause cell death in two phases. The initial insult can cause immediate neuronal demise, however, a secondary process also causes significant neuronal loss for approximately 72 hours after the initial event. In this period, two physiologic changes occur. Beginning 6 hours after the injury, the cells' injured mitochondria begin to fail and cannot meet the metabolic needs of the cell. At the same time, neuronal cells become hyper-excitatory and begin to accumulate calcium, produce oxygen free radicals and excitotoxins, and form nitric oxide within the cells, all of which lead to cell death. Perlman also found an increased rate of apoptosis (spontaneous cell death) after neurologic injury. This evidence is significant as Marret et al. (2007) found MgSo4 adminstration to have multiple neuroprotective roles after a neurologic insult in rats, pigs, and mice. These effects include decreased excitotoxin release, decreased apoptosis, prevention of modification of the nuclear cell membrane, and over-all improvement in neurologic function (Marret et al., 2007). These findings, as well as a growing

need to decrease neurologic sequelae in pre-term infants, have led to multiple studies of MgSo4 in humans.

Literature Review

Despite many attempts at finding therapies to reduce the rates of CP and neurologic injury both pre and postnatally, few have proven successful in randomized, controlled trials (Marret, Doyle, Crowther, and Middelton, 2007). However, several observational studies conducted during the 1980's and 1990's showed infants whose mothers received MgSo4, either as a tocolytic agent or to manage pre-eclampsia, had a markedly decreased risk of developing CP (Nelson and Grether, 1995; Stanley and Crowther, 2008). These finding were largely re-affirmed in multiple prospective, randomized trials conducted from 1995-2008. Four of five studies conducted administered MgSo4 specifically for neuroprophylaxis, the fifth (MAGPIE) studied the efficacy of MgSo4 as treatment for pre-eclampsia, but also measured neurologic outcomes (Cahill, 2010; Marret et al., 2007). These studies are individually reviewed below.

The largest study, Beneficial Effects of Antenatal Magnesium Sulfate (BEAM), was conducted from 1997-2007 (Rouse, Hirtz, Thom, Varner, Spong, 2008). The study included 2471 women presenting from 24.0 to 31.6 weeks gestation with advanced preterm labor or premature rupture of the membranes and no recent exposure to magnesium sulfate. Participants were randomized to receive either intravenous magnesium sulfate or masked study drug placebo. Those receiving MgSo4 were given a 6 gram loading dose followed by a 2 gram/hour infusion (or equivalent rate for placebo). If after 12 hours, delivery did not occur and was not anticipated, the infusion was stopped. Standard clinical management and therapy was maintained for all study patients.

Rouse et al., (2008), found fetal exposure to magnesium sulfate before anticipated preterm delivery did not reduce the combined risk of moderate or severe cerebral palsy or death (11.3% and 11.7%, respectively; relative risk, 0.97; 95% confidence interval [CI], 0.77 to 1.23), but did reduce the rate of CP among survivors (1.9% vs. 3.5%). The risk of death did not differ significantly between the groups (9.5% vs. 8.5). No woman had a life-threatening event during the trial.

The PreMAG study (Marret, Marpeau, and Benichou, 2008) was conducted in France from 1997-2003 on women less than or equal to 33 weeks gestation. The trial enlisted 286 and 278 women, respectively, who were randomly assigned to receive a single infusion of 4 gm of $MgSO_4$ or 0.9% saline. Pediatricians, who were blinded to treatment, evaluated motor and cognitive functions by using a questionnaire with developmental items extracted from the Amiel-Tison and Denver scales and the European Cerebral Palsy Network definition (Marret et al., 2008). When direct examination was not possible, assessment was performed through parent telephone interview. All assessments were completed at 24 months of age.

Results of the PreMag study showed a statistically significant decreases in both death or CP (16.1% Vs 20.2%, respectively), as well as a decrease in CP over-all (7% Vs. 10.2%, respectively). Also important, the PreMag study demonstrated no increase in maternal or pediatric mortality (Marret et al., 2008).

The ACTOMgSO4 trial (Crowther, Hiller, Doyle, and Haslam, 2003), was conducted from 1996-2000 in New Zealand and Australia and had a total of 1062 women enrolled. All enrollees were less than 30 weeks gestation and expected to give birth within 24 hours. Participants in the experimental group received a 4g loading dose of MgSo4 followed by

1g/hour maintenance until birth. Those in the control group received an equal volume of saline. Survivors were examined until they reached 2 years of age by pediatricians and psychologists. The study found pediatric mortality, defined as total number deaths prior to exam at 24 months of age, was reduced (13.8% from 17.1%), as well as combined death or CP (19.8% from 24.0%), however, neither were statistically. None-the-less, findings of substantial gross motor dysfunction and combined death or substantial gross motor dysfunction were reduced at statistically significant levels (3.4% Vs. 6.6% and 17.0% Vs. 22.7 %, respectively).

The MAGPIE study (Altman, Carroli, Duley, Farrell, Moodley, et al., 2002), was conducted from 1998 to 2001 with a total of 10,141 women enrolled. The trial was not focused on MgSo4 as a neuroprotective agent, but on MgSo4 as an effective treatment for pre-eclampsia. This study enrolled women who were expected to give birth within 24 hours of admission. An initial dose of 4 gm MgSo4 was given initially followed by 1gm/hr drip over 24 hours of a series of 5 gm intramuscular injections (IM) given every 4 hours. The placebo group received an identical volume of saline given over the same schedule. While the primary focus of MAGPIE was maternal health, the authors also included information on fetal neuroprotection for infants born at less than 34 weeks gestation (n= 805).

Results from the MAGPIE study neither supported nor contradicted the use of MgSo4 for neuroprotection. Prevalence of CP in the treatment group was 3% vs. control 3%, and the outcome of death or CP 41.8% in the treatment group and 40.1% in the control (Altman et al., 2002). Importantly, the MAGPIE study demonstrated no statistically significant increase in mortality among treated infants. However, treatment was associated with a 5 % increase in C-section rate.

The MagNET study (Mittendorf, Dambrosia, Pryde, Lee, Gianopoulos, 2002), conducted from 1995-1997 had a total enrollment of 149 women who were between 25 and 33 weeks gestation and in pre-term labor. The study had two arms, a tocolytic arm and a preventative arm. Women dilated less than 4 cm were included in the tocolytic arm and received either 4gm bolus of MgSo4 followed by 2-3 gm/hour maintenance or an alternative tocolytic. Women dilated to 4 or greater were in the preventative group and received either a 4 gm MgSo4 bolus or saline placebo. This trial was terminated prematurely due to concerns the treatment group had increased mortality (N= 10, 11.8% in treatment group versus 1 or 1.2% in the placebo group. Increased infant mortality was only noted in the tocolytic arm, which required longer (unlimited) courses of treatment. This was the only study to show a statistically significant increase in infant mortality rates among infants treated with MgSo4. Results of all five trials are listed in table 1-1 below.

Table 1-1: Rates of pediatric mortality, cerebral palsy and death or cerebral palsy in randomized controlled trials of antenatal magnesium sulfate therapy where fetuses were <34 weeks gestational age at randomization (adapted from Marret et al, 2007).

Study (ref. no.)	Randomized		Mortality		Cerebral palsy		Death or cerebral palsy	
	M: n =	C: n =	M: n =	C: n=	M: n =	C: n=	M: n =	C: n=
MagNET 2002	85	80	11.8% (10)	1.2% (1)	3.5% (3)	3.8% (3)	15.3% (13)	5.0% (4)
ACTOMgSO$_4$ 2003	629	626	13.8% (87)	17.1% (107)	5.7% (3)	6.7% (42)	19.6% (123)	23.8% (149)
BEAM 2004	1041	1095	9.5% (99)	8.5% (93)	2% (20)	3.4% (38)	11.2% (118)	11.9% (131)
MAGPIE 2006	404	401	41.3% (167)	39.4% (158)	0.5% (2)	0.7% (3)	41.8% (169)	40.1% (161)
PreMag 2006	352	336	9.4% (33)	10.4% (35)	6.2% (22)	7.4% (25)	15.6% (55)	17.9% (60)

Several meta-analyses have also been completed to assess the efficacy and safety of MgSo4 prior to preterm birth. This review includes a Cochrane review, as well as three others, all of which analyzed the same five clinical trials using the primary outcomes of fetal or infant demise by 1 year of age, CP, moderate to severe CP, and a composite outcome of death or CP by 2 years of age. For this analysis, outcomes were sub-categorized into trials looking at MgSo4 specifically for neuroprotection, and MgSo4 given for other maternal indications such as hypertension or seizure prophylaxis. All included meta-analyses, summarized below, came to similar conclusions and support the use of MgSo4 for antenatal neuroprotection.

When all five trials are considered, using antenatal MgSo4 had no significant effect on the combined outcome of death or CP (RR 0.94; 95% CI 0.78-1.12) (Simhan and Himes, 2010).

However, for the four trials designed to specifically assess neuroprotective effects of MgSo4, there was a significant reduction in death or CP (RR 0.85; 95% CI 0.74-0.98). There was no significant effect on pediatric mortality rates in either subgroup. There was a significant reduction in the risk of cerebral palsy (overall RR 0.68; 95% CI 0.54-0.87; neuroprotection trials subgroup RR 0.71; 95% CI 0.55-0.91) and of moderate to severe CP in the neuroprotection trials subgroup (RR 0.64; 95% CI 0.44-0.92). The absolute risk of CP was 3.7 percent for fetuses exposed to MgSo4 versus 5.4 percent for unexposed fetuses, giving an absolute risk reduction of 1.7 percent (Simhan and Himes, 2010). There was also a reduction in risk of substantial gross motor dysfunction (overall RR 0.61; 95% CI 0.44-0.85; neuroprotection trials subgroup RR 0.60; 95% CI 0.43-0.83), but not in any other neurological outcome.

It is worth noting that there were competing outcomes noted in these analyses, specifically the finding of no significant effect of MgSo4 on the combined outcome of death or CP in the overall group of trials and in the subgroup looking exclusively at trials for neuroprotection. Simhan and Himes (2010), believe it is possible that the lack of statistical significance of the combined outcome is due to an increased risk of death in a subgroup of fetuses or infants, as suggested by two trials. While this finding should give providers pause, increased mortality has not been demonstrated in other clinical trials of MgSo4, including the MAGPIE trial, which had over 10,000 participants (Altman et al., 2002). It should be noted, too, that the combined outcome of "death or cerebral palsy" was reduced significantly when only trials designed specifically to assess the neuroprotective effect of magnesium sulfate were

analyzed (Simhan and Himes, 2010). One factor that might be considered when weighing the risk and benefit of antenatal MgSo4 therapy for neuroprotection is gestational age.

A meta-analysis by Cahill et al., 2010, concluded that MgSo4 can reduce the risk of CP, particularly in infants born at or below 32 weeks gestation. Cahill acknowledges that, while much data is still needed in regard to the use of MgSo4 for neuroprotection, it has been proven safe over decades of perinatal use and should be considered for neuroprotection in infants less than 32 weeks gestation, an age where the number of infants needed to treat (NNT) to prevent one case of CP is relatively low. Table 2-1, below, illustrates the inverse relationship between the NNT with MgSo4 and gestational age at birth. Table 2-1 also outlines a summary of baseline risk that an infant will develop CP based on gestational age if no treatment were given.

Table 2-1: Illustration of numbers needed to treat with MgSo4 stratified by gestational age (Cahill et al., 2010)

Gestational age (weeks)	Baseline risk CP (%)	Risk CP with MgSo4 (%)	Risk Difference (%)	Number Needed to treat
22-27	14.6	8.0	6.6	15
28-31	6.2	3.4	2.8	35
32-36	0.7	0.4	0.3	333
>37	0.11	0.06	0.05	2000

Treatment Risks

While three of the five original research trials, as well as the authors of all four meta-analyses, recommend use of antenatal MgSo4 as a neuroprophylactic treatment, it is not without risks. Crowther et al., (2010) found multiple adverse effects in women receiving the MgSo4 treatment including flushing, sweating, nausea, vomiting, headache, and tachycardia. All of these side-effects were temporary and resolved after treatment was ceased. Infants born to mothers treated with MgSo4 also risk temporary side effects such as decreased tone and poor feeding (Macdonald, Mullett, and Seshia, 2005). Importantly, only the MagNet study showed an increased risk of mortality with MgSo4 administration and that increase was only noted in the prophylaxis group (Mittendorf et al., 2002). Cahill (2010) also points out that there is inherent risk in using a therapy in which the mechanism of action is not well understood. None-the-less, as the number of pre-term births and the prevalence of CP among premature infants rises, so do the potential benefits of MgSo4, particularly in infants less than 32 weeks gestation.

Implications and Recommendations

As improvements in medical care and technology continue to lower fetal age of viability and increase the number of infants who survive severe neurologic injuries, it is urgent to find therapies to prevent the crippling, life-long effects of CP. While additional research is needed to better understand the precise ways in which MgSo4 affects the brain, the safety of MgSo4 has long been established in maternal-fetal medicine (Altman et al., 2002). Given the research cited above, as well as a recommendation by the World Health Organization, it may be appropriate for providers to consider MgSo4 for nueroprophylaxis on a broader scale (Lumbiganon, 2009). Because no widely accepted guidelines exist for neuroprotective MgSo4 therapy at this point, it

may be advisable to follow guidelines used in successful clinical trials. Also, because both risk of CP and efficacy of treatment are diminished in infants greater than 32 weeks gestation, MgSo4 neuroprophylaxis should only be attempted with infants less than 32 weeks.

As outlined in the BEAM trial (Rouse, et al., 2008), and PreMag (Crowther et al., 2003) a loading dose of 4 gm should be administered followed by a 1 mg/hour infusion up to 24 hours. If labor ceases, the therapy should be stopped but may be re-started if labor resumes before the patient reaches 32 weeks gestation (Rouse et al., 2008). More data is needed to determine risks and efficacy of treatment in cases of high risk maternal conditions such as pre-eclampsia, abruption, and others. Use of prophylactic MgSo4 in these patients should be avoided until further data is collected.

Parent Education

Because MgSo4 is relatively new and it's physiologic mechanisms poorly understood, involving parents in the decision to use prophylaxis is essential. This can be complicated as there are few resources available to parents regarding MgSo4 neuroprophylaxis. This makes a private and detailed provider consult invaluable. The consult should be performed by a physician familiar with current literature regarding MgSo4 neuroprophylaxis, and should be presented in relation to the family's specific risk factors, such as the infant's gestation and corresponding risk of CP. This should be a realistic discussion of the potential benefits and side-effects of MgSo4 administration. Parents should be encouraged to ask questions and repeat back what they understand the risks and potential benefits to be. Once the initial consult is completed, the parents can be referred to websites such as the March of Dimes http://www.marchofdimes.com/birthdefects_cerebralpalsy.html and "4 My Child"

http://www.cerebralpalsy.org/cerebral-palsy-causes/premature-birth/ to assist parents in understanding the various risk factors associated with pre-term birth, the range of disabilities associated with CP, as well as finding reassurances they (the parents) did not do anything to "cause" their child to have CP. This is a difficult position for providers as it is important for parents to understand the risks to their baby, but the information needs to be provided in a way that does not induce panic in the parents.

Conclusion

Premature birth is becoming more common with infants surviving birth at extremely young ages (Crowther, 2010). Many of these extremely premature infants' baseline risk of CP is nearly 20% with no prophylactic treatments available. Decades of MgSo4 use in obstetric care, as well as a preponderance of evidence gathered in the trials discussed above, have demonstrated the risk of MgSo4 therapy to be minimal, and side-effects reversible. This must be weighed against the risk for CP which can be substantial and the associated handicaps irreversible. Available evidence suggests neuroprophylactic MgSo4 provides a reasonable chance to prevent one of the most common and debilitating conditions associated with prematurity and should be offered to parents who face imminent delivery of an extremely premature infant.

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