Prevention and Tocolytic Agents 2

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Abstract

Preterm birth is the single most important determinant of adverse infant outcomes, in terms of survival and quality of life. Preterm infants are particularly vulnerable to complications with the increasing contribution of neonatal deaths to overall child mortality. Infant mortality and morbidity from preterm birth can be reduced through interventions given to the mother before or during pregnancy, and to the preterm infant after birth. The most beneficial interventions are those that aim to improve outcomes for preterm infants when preterm birth is inevitable. Magnesium sulfate ($MgSO_4$), one of the most commonly used tocolytic agents, has been used in obstetrics for decades, and thousands of women have been enrolled in clinical trials to study the efficacy of prenatal $MgSO_4$ for a variety of conditions including recent studies that demonstrated neuroprotective effects in infants with eclampsia. The uses of $MgSO_4$ in the context of appropriate clinical obstetric practice include fetal neuroprotection before anticipated early preterm (<32 weeks of gestation) delivery. $MgSO_4$ also may be used to prolong the pregnancy to allow for the administration of antenatal corticosteroids between 24 and 34 weeks of gestation.

Keyword

Long-term tocolysis · Preterm delivery · Magnesium sulfate · Neuroprotection

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11.1 Introduction

Preterm birth is a major cause of neonatal death and is associated with several short- and long-term infant morbidities. Tocolytics, which act to inhibit uterine contractions, are commonly used to prevent or delay preterm birth [1]. $MgSO_4$ is one of the most commonly used tocolytics. We herein discuss the use of $MgSO_4$ in the management of premature labor and its neuroprotective effects [2].

11.2 Mechanism of Action

11.2.1 Biological Properties

Magnesium is the fourth most abundant ion in the human body and contributes to several physiological processes, including storage, metabolism, and energy utilization. Magnesium ion is indispensable for DNA, RNA, and protein synthesis. It contributes to glycolysis and adenosine triphosphate (ATP) production and functions as a cell membrane stabilizer. It also plays important roles in the cardiac function, muscle contraction, vascular tone, nerve impulses through its physiological role as a calcium channel blocker [3], and the regulation of sodium and potassium flow through its action on ion pumps, for example, Na+/K+ ATPase and other membrane receptors, including nicotinic acetylcholine receptors [4]. In the brain, magnesium is mainly bound to chelating agents, such as ATP, and is a cofactor in more than 300 enzymatic reactions [5]. In the central nervous system, magnesium is a noncompetitive blocker of N-methyl-aspartate (NMDA) glutamate receptor and regulates calcium influx [3]. Sixty percent of magnesium is stored in the bone, 20% in muscle, and 20% in soft tissue. Magnesium is mainly present in an ionized state (60%) but may form complexes with proteins (33%) or anions (7%). The normal plasma magnesium concentration is 0.45–1.05 mmol/L in adults [6], while that in the first week of life in newborns is 0.55–1.26 mmol/L [7].

11.2.2 Uterine Contraction

The mechanism of magnesium's effects on uterine contraction has not been completely elucidated despite more than 40 years of studies on the topic. At the level of voltage-gated channels on plasma membranes, magnesium probably competes with calcium. It hyperpolarizes the plasma membrane and inhibits myosin light-chain kinase activity by competing with intracellular calcium at this site. The inhibition of myosin light-chain kinase activity reduces myometrial contractility [8–10].

11.2.3 Neuroprotection

Magnesium has several biological effects that may contribute to protecting the preterm neonatal brain [11]; however, the precise mechanism underlying its neuroprotective effects is unknown. The most common pathological lesion associated with

cerebral palsy in preterm infants is periventricular white matter injury [12]. Oligodendrocytes constitute the major glial population in white matter. NMDA receptors on oligodendrocytes play an important role in the glial injury process. NMDA receptor antagonists have been shown to be potent neuroprotective agents in numerous animal models of perinatal brain injury. $MgSO_4$ acts as a calcium antagonist reducing calcium influx into cells [13, 14], which may reverse the adverse effects of hypoxia/ischemic brain injury by blocking NMDA receptors. $MgSO_4$ is also involved in the protection of tissue against free radical activity [13], acts as a vasodilator [15], reduces vascular instability, prevents hypoxic injury, attenuates cytokine or excitatory amino acid-induced cytotoxicity [16], and has anti-apoptotic actions [17].

11.3 Preclinical Study

Since the 1980s, animal experiments have studied the neuroprotective effects of magnesium. The initial studies included adult animal models of hypoxia, stroke, and traumatic brain injury [18]. In 1989, McIntosh et al. demonstrated that the post-traumatic injection of $MgSO_4$ reduced neurological disorders in a dose-dependent manner in a rat brain injury model [19].

In 1996, Marinov et al. proved that the neuroprotective effect of intraarterial $MgSO_4$ in rats with reversible focal ischemia was dose-dependent and related to the duration of ischemia by blocking the NMDA receptor [20]. The neuroprotective effects of $MgSO_4$ on the developing brain have been examined in several animal models. The importance of the timing of $MgSO_4$ administration has been reported. The intraperitoneal administration of $MgSO_4$ was shown to reduce the excitotoxic brain lesions in mice induced by the intracerebral injection of ibotenate (a glutamate receptor agonist) until postnatal day (P)5—which was comparable to brain lesions in humans at 32 weeks of gestation (WG) [21]. In this P5 (32 WG) model, $MgSO_4$ prevented movement disorder, fine motor skill change, and memory impairment in adolescent mice [22]. With the Rice–Vannucci procedure (surgical ligation of the right carotid artery followed by exposure to 8% oxygen for 1–2 h) of focal hypoxic-ischemic encephalopathy in the rat, $MgSO_4$ injection prior to the hypoxic episode on P7 resulted in the reduction of lesion size, hippocampal apoptosis, and the improvement of adult sensorimotor performance [17, 23]. In this model, $MgSO_4$ preserved mitochondrial respiration and reduced inflammation, thus decreasing the production of reactive oxygen species after hypoxic ischemia [24]. Our group has also reported the effect of magnesium during perinatal period for the past 20 years. First, we used chronically catheterized goat fetuses that were directly infused with either magnesium or normal saline for 4 h. The infusion of $MgSO_4$ significantly decreased the baseline fetal heart rate (FHR), short-term variability, long-term variability, and reactivity in the FHR patterns of goats at 0.85 gestation [25]. The FHR was significantly decreased by hypoxemia with increase in variability in controls. In the magnesium group, the FHR was not significantly decreased by hypoxemia. Acute hypoxemia also increased the FHR variability during magnesium infusion, which was significantly reduced in comparison to that in the control population

[26]. Second, in the P7 rat, the long-term administration of $MgSO_4$, which lasted for three consecutive days, inhibited caspase-3 activation and MAP-2 immunostaining, and resulted in significantly decreased cyst formation from necrosis, and significantly decreased neuronal loss in the cerebral cortex and the hippocampus. These results suggested that magnesium inhibited apoptotic neuronal death of hypoxia-ischemia and the neuroprotective effects against hypoxia-ischemia [27, 28]. The neuroprotective effect of $MgSO_4$ was also assessed under inflammatory conditions using a mouse model in which preterm birth mouse was induced by the administration of lipopolysaccharide and showed that $MgSO_4$ ameliorated neuronal injury in inflammation-associated preterm birth, which may have a preventive effect against cerebral palsy [29].

11.4 Clinical Effects in Pregnancy

11.4.1 Tocolytic Agents

For several decades, $MgSO_4$ has been used in obstetrics as a tocolytic agent and for the prevention or treatment of eclampsia [30, 31]. Contrary to the strong evidence indicating its effectiveness in preventing eclampsia, $MgSO_4$ is ineffective in treating preterm birth. In 2014, in a systematic review of randomized studies comparing $MgSO_4$-treated non-treated/placebo-controlled groups, Crowther et al. reported that the administration of $MgSO_4$ was associated with a significant reduction of births within 48 h of study initiation (RR, 0.56, 95% CI, 0.27–1.14; targeted at 182 women), with no improvement in the neonatal or maternal outcomes. The efficacy of $MgSO_4$ was not significantly different from that of other tocolytic agents (beta mimetic, calcium antagonist, Cox inhibitor, prostaglandin inhibitor, human chorionic gonadotropin) in 33 comparative trials [32]. The American College of Obstetricians and Gynecologists and Society for Maternal-Fetal Medicine regard $MgSO_4$ as an option for the short-term prolongation of pregnancy (up to 48 h) and recommended the administration of antenatal corticosteroids to pregnant women at risk for preterm delivery within 7 days [33]. According to a systematic review of randomized trials, after the acute prevention of preterm labor, maintenance tocolysis with $MgSO_4$ did not prolong pregnancy, prevent preterm birth, or improve neonatal outcomes in comparison to placebo/non-treatment [34].

11.4.2 Neuroprotective Effects

In the late 1990s, some observational studies discussed the effects of $MgSO_4$ on neurological outcomes in preterm infants. Nelson and Gather reported that exposure to $MgSO_4$ was higher in the control group than in a group of children with cerebral palsy (odds ratio [OR], 0.14; 95%CI, 0.05–0.51) [35]. A meta-analysis of these

observational studies focused on the finding that antenatal $MgSO_4$ treatment was associated with a significantly reduced risk of mortality (risk ratio [RR], 0.73; 95% CI, 0.61–0.89) and cerebral palsy (OR, 0.64; 95% CI, 0.47–0.89) [36]. Antenatal $MgSO_4$ treatment was also associated with a decreased incidence of apparent echodensity and echolucency on neonatal cranial ultrasonography and cerebellar hemorrhage on MRI [37, 38].

11.4.2.1 Randomized Controlled Trials (RCTs)

There have been three major trials designed solely to assess the neuroprotective benefits of $MgSO_4$ with significant heterogeneity: the Australasian Collaborative Trial of Magnesium Sulfate (ACTOMgSO_4) [39], the Beneficial Effects of Antenatal Magnesium Sulfate (BEAM) trial [40], and the PREMAG trial [41]. These trials are summarized in Table 11.1. As cerebral palsy and death are competing outcomes, it is important to use the combined outcome of "cerebral palsy or death."

Table 11.1 RCTs to assess the neuroprotective effect of $MgSO_4$

Trial	Number of subjects	GW at randomization	$MgSO_4$ dose	Death	Cerebral palsy	Composite outcome
ACTOMgSO_4	1062	<30	4 g loading dose followed by 1 g/h for maximum of 24 h	13.8 vs 17.1% RR 0.83 [0.64–1.09]	6.8 vs 8.2% RR 0.83 [0.54–1.27]	Death or cerebral palsy: 19.8 vs 24.0% RR 0.83 [0.66–1.03]
BEAM	2241	24–31	6 g loading dose followed by 2 g/h for maximum of 12 h	9.5 vs 8.5% RR 1.12 [0.85–1.47]	Moderate to severe cerebral palsy: 1.9 vs 3.5% RR 0.55 [0.32–0.95[a]]	Stillbirth, infant death by 1 year, moderate to severe cerebral palsy >2 years of corrected age: 11.3 versus 11.7% RR 0.97 [0.77–1.23]
PREMAG	573	<33	4 g loading dose No maintenance dose			Death or cerebral palsy: OR 0.65 [0.42–1.03] Severe motor dysfunction or death: OR 0.62 [0.41–0.93]

GW gestational week, *RR* relative risk, *OR* odds ratio

[a]Only infants of pregnancies randomized at <28 weeks had a significant reduction in moderate or severe cerebral palsy

Australasian Collaborative Trial of Magnesium Sulfate (ACTOMgSO$_4$)
A total of 1062 women in preterm labor before 30 WG from 16 centers were included in the Australasian Collaborative Trial of Magnesium Sulfate (ACTOMgSO$_4$) between February 1996 and September 2000. MgSO$_4$ (4 g loading followed by 1 g/h maintenance for 24 h or until birth) was randomly allocated to 535 women (629 live fetuses), while 527 women (626 live fetuses) received placebo. The primary study outcome, which was the rate of cerebral palsy, indicated no significant difference between the two groups (6.8% in the MgSO$_4$ group versus 8.2% in the control group; RR, 0.83; 95% CI, 0.54–1.27); however, the rate of motor dysfunction was significantly lower in the MgSO$_4$ group (3.4 versus 6.6% in the control group; RR, 0.51; 95% CI, 0.29–0.91).

The Beneficial Effects of Antenatal Magnesium Sulfate (BEAM)
The BEAM trial included 2241 women with preterm labor before 32 WG who were managed at 20 facilities between December 1997 and May 2004. They were randomized to receive a 6 g bolus of MgSO$_4$ followed by a 2 g/h maintenance dose for 12 h (1096 women, 1188 fetuses) or placebo (1145 women, 1256 fetuses). The rates of pediatric mortality did not differ between the two groups to a statistically significant extent. Although the primary outcomes (composite of stillbirth or death by 1 year or cerebral palsy at 2 years) were similar in the two groups, the incidence of moderate or severe cerebral palsy was significantly reduced in the MgSO$_4$ group (1.9 versus 3.5%; RR, 0.55; 95% CI, 0.32–0.95).

PREMAG Trial
The PREMAG trial included 564 women treated at 18 French centers between July 1997 and July 2003, with 286 women (354 fetuses) randomly assigned to receive a 4 g bolus of MgSO$_4$ and 278 women (341 fetuses) who were randomly assigned to receive placebo. The trial was discontinued after 6 years of enrollment. The primary outcomes (the rates of white matter injury and mortality) were similar between the groups (white matter injury, 10.0% versus 11.7%; OR, 0.78; 95% CI, 0.47–1.31; mortality, 9.4 versus 10.4%; OR, 0.79; 95% CI, 0.44–1.44). The rate of combined death or gross motor dysfunction at 2 years was lower in the MgSO$_4$ group (25.6 versus 30.8%; OR, 0.62; 95% CI, 0.41–0.93), but there was no difference in the incidence of cerebral palsy [42].

11.4.2.2 Meta-Analyses

Five RCTs [12, 43–46] have been the focus of four meta-analyses with consistent findings and conclusions (Table 11.2). In all meta-analyses, the antenatal administration of MgSO$_4$ to women at risk of preterm delivery was associated with a significantly reduced risk of cerebral palsy in children exposed in utero, with an RR ranging from 0.61 to 0.70 and no effect on mortality. The number of women needed to treat (NNT) to avoid one case of cerebral palsy ranged from 46 to 74 in infants born before 34 WG. Mild maternal side effects (e.g., flushing, nausea or vomiting, sweating, injection site discomfort) were more frequent in the MgSO$_4$ groups, but there were no significant severe side effects. Furthermore, an individual participant

Table 11.2 Main outcomes of the meta-analyses

Authors	Published year	Pediatric mortality[a]	Cerebral palsy[a]	Death or cerebral palsy[a]	NNT to avoid one cerebral palsy[b]
Doyle et al. [44]	2009	1.04 [0.92–1.17]	0.68 [0.54–0.87]	0.94 [0.78–1.12]	63 [43–115]
Conde-Agudelo and Romero [12]	2009	1.01 [0.89–1.14]	0.69 [0.55–0.88]	1.01 [0.89–1.14]	74 [41–373]
Costantine and Weiner [45]	2009	1.01 [0.89–1.14]	0.70 [0.55–0.89]	0.92 [0.83–1.03]	<30WG: 46 [26–187] 32–34 WG: 56 [34–164]
Zeng et al. [46]	2016	0.92 [0.77–1.11]	Moderate to severe: 0.61 [0.42–0.89]	N/A	N/A
Crowther et al. [47] (individual participant data analysis)	2017	1.03 [0.91–1.17]	0.68 [0.54–0.87]	0.86 [0.75–0.99]	46 [not shown]

NNT number needed to treat
[a]Relative risk [95% confidence interval]
[b]Number [95% confidence interval]

data meta-analysis was undertaken by the AMICABLE group (Antenatal Magnesium sulfate Individual participant data international Collaboration: Assessing the benefits for babies using the Best Level of Evidence) to explore the interaction between treatment and participant characteristics (Table 11.2), which included the five RCTs (5493 women and 6131 babies). The overall RR for cerebral palsy among survivors after the antenatal administration $MgSO_4$ was 0.68 (95% CI, 0.54–0.87), and the NNT was 46. Interestingly, $MgSO_4$ also reduced the combined risk of fetal, infant death, and cerebral palsy in the analysis of the four trials with fetal neuroprotective intent (RR 0.86, 95% CI, 0.75–0.99) [47]. In all RCTs and meta-analyses to date, $MgSO_4$ treatment did not affect pediatric mortality or neonatal morbidity (respiratory distress syndrome, chronic lung disease, any intraventricular hemorrhage, cystic periventricular leukomalacia, necrotizing enterocolitis, patent ductus arteriosus, and retinopathy of prematurity). Similarly, $MgSO_4$ treatment was not associated with serious maternal side effects. The benefit remained constant regardless of gestational age, cause of prematurity, total dose received, and the maintenance dose administered after the loading dose.

11.5 Clinical Approach and Long-Term Tocolysis

Women at high risk of imminent preterm birth are appropriate candidates for $MgSO_4$ for protection from brain damage. None of the randomized trials of $MgSO_4$ for neuroprotection included pregnancies at <24 WG. The upper limit of gestational age for the neuroprotective effect of antenatally administered magnesium has not been well-studied [45]. In 2018, the American College of Obstetricians and

Gynecologists and the Society for Maternal-Fetal Medicine commented that they continue to support the short-term (usually <48 h) use of $MgSO_4$ in obstetric care for appropriate conditions and for appropriate durations of treatment, which includes the prevention and treatment of seizures in women with preeclampsia or eclampsia, fetal neuroprotection before anticipated early preterm (<32 WG) delivery, and short-term prolongation of pregnancy (up to 48 h) to allow for the administration of antenatal corticosteroids in pregnant women who are at risk of preterm delivery within 7 days [33]. The intrapartum administration of $MgSO_4$ to women with growth-restricted fetuses born at <29 weeks' gestation was associated with reduced odds of composite of death or significant neurodevelopmental impairment (adjusted OR, 0.42; 95% CI, 0.22–0.80) [48]. We favor the administration of a 4 g loading dose of $MgSO_4$ for 30 min and a maintenance dose of 1 g/h. Our group has already reported that among infants born between 28 and 32 WG survivors in the low-dose group (total $MgSO_4$ administration <50 g) had significantly reduced rates of cerebral palsy (OR 0.4, 95% CI, 0.2–0.98) and brain damage (OR 0.2, 95% CI, 0.1–0.9) [49].

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