

**Magnesium as an adjunct to therapeutic hypothermia: a review of its use in the fetus, term infant with neonatal encephalopathy and the adult stroke patient**

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## **Abstract (500 words)**

Magnesium is an intracellular cation essential for many enzymatic processes and cellular functions. This article explores the possibility of magnesium being used as an adjunct to hypothermia in postnatal term neonatal encephalopathy. There are three basic lines of evidence for magnesium sulfate as a neuroprotective agent. 1) Animal studies of neonatal encephalopathy (NE) at term equivalent age have been confounded by concomitant hypothermia induced by magnesium itself. 2) The combination of magnesium and cooling has been shown to be more effective than either treatment alone in adult rodents. 3) In preterm gestation, magnesium sulfate given antenatally in threatened preterm labor has demonstrated a significant reduction in the risk of cerebral palsy at 2 years of age, though the benefit is not clear at school age. Against the use of magnesium sulfate as a neuroprotective strategy are disappointing results in adult studies in ischemic and hemorrhagic stroke. Furthermore, the neurological scores may be affected by the increased hypotonia observed.

The theoretical basis of magnesium sulfate is that it acts as an endogenous calcium channel antagonist at neuronal synapses, thought to prevent excessive activation of N-methyl-D-aspartate (NMDA) receptors by excitatory amino acids, such as glutamate, and by down-regulation of pro-inflammatory pathways. The immature brain is particularly prone to excitotoxicity and inflammation has been strongly implicated in the pathogenesis of cerebral palsy. Early intervention is essential in the prevention of the secondary phase of neuronal injury.

Magnesium sulfate may be considered as a neuroprotective agent given its favorable safety profile, relative inexpensive and widespread availability.

## INTRODUCTION

Magnesium is an ionized mineral essential to hundreds of enzymatic processes, including hormone receptor binding, energy metabolism, muscle contractility as well as neuronal and neurotransmitter function[1]. It is primarily an intracellular cation and stores are distributed between bone (53%), muscle (27%) and soft tissue (19%). Serum magnesium levels are tightly controlled (0.65 – 1.05 mmol/L) and homeostasis is maintained through intestinal absorption, storage in bones and renal excretion[1,2]. Magnesium has an inhibitory effect at neuronal synapses, leading to its use as an anticonvulsant, particularly in eclamptic seizures[3]. [We present three lines of evidence to support the possible use of magnesium sulfate as adjunct to hypothermia for term neonatal encephalopathy and leave it to the reader to judge for themselves whether the evidence is sufficient; i\) studies in term neonates with neonatal encephalopathy \(NE\), ii\) studies in antenatal use for preterm delivery and iii\) adult brain injuries.](#) This article explores the neuroprotective potential of magnesium, its mechanism of action and efficacy in different patient populations and neurological disorders.

### *Role of magnesium in cellular metabolism*

Magnesium is an important co-factor in over 300 enzymatic reactions and is essential to normal cellular function. Magnesium acts as a counter ion for ATP and stabilizes many ATP-dependent processes, including glucose utilization, protein and nucleic acid synthesis[4]. It contributes to the structural integrity of nucleic acids, proteins and mitochondria[5].

As an endogenous calcium antagonist, magnesium serves a number of regulatory roles at neuronal and neuromuscular synapses. It blocks calcium entry at the presynaptic junction, preventing excessive acetylcholine release and stimulation at the neuromuscular junction. It also has a depressant effect at the post-synaptic membrane through the voltage dependent block of N-

methyl-D-aspartate (NMDA) receptors[1]. This action as an NMDA receptor antagonist underpins one of the main proposed mechanisms of magnesium neuroprotection.

### *Excitotoxicity*

The precise mechanism by which magnesium provides neuroprotection has not been well established. One of the most commonly held theories is that magnesium prevents excitotoxic damage through NMDA receptor blockade. This post-synaptic receptor normally strengthens synaptic connections when repeatedly activated (long-term potentiation) and plays a crucial role in memory function[6]. Activation of the NMDA receptor by excitatory neurotransmitters permits the influx of calcium ions, serving as secondary messenger for physiological cell processes e.g. regulation of transcription factors and DNA replication[7,8].

Neurons exposed to hypoxic stress are unable to maintain normal glutamate homeostasis, resulting in excessive stimulation of NMDA receptors. This results in a cascade of 'excitotoxic' events causing acute cell swelling and delayed cell degeneration[9]. This delayed neuronal injury is mediated by excessive calcium influx in to the cell, triggering catabolic enzymes (e.g. proteases, phospholipases, endonucleases) and free radical production (Fig 2). Glutamate excitotoxicity and the loss of intra-cellular calcium homeostasis also triggers cellular 'suicide' programs, leading to apoptosis[9].

The NMDA receptor itself is composed of four subunits (heterotetramer), similar to a hemoglobin molecule. Receptors subunits containing NR2B have a high permeability to calcium[10] and are particularly abundant in preterm white matter[11]. While this may serve an important role during the rapid growth and myelination in early neuronal development, it may also confer particular vulnerability to preterm white matter. This may explain in part the different patterns of injury between preterm and term hypoxia ischemia[8,12].

Magnesium is an endogenous calcium antagonist and provides a voltage dependent blockade of the NMDA receptor. Through inhibiting the rapid influx of calcium, magnesium may prevent the secondary cascade of injury that leads to cell death[1]. This theory is supported by preclinical data, both in vitro and in vivo. Magnesium has been shown to reduce excitotoxic damage induced in mice by ibotenate, a glutamatergic agonist[13]. Extracellular levels of glutamate are reduced in magnesium treated gerbils following focal cerebral ischemia[14]. Furthermore, incubation of primary oligodendrocyte precursor cells with magnesium appears to improve cell survival following oxygen glucose deprivation[15].

The extent of injury secondary to excessive NMDA receptor activation however remains controversial. Alternative NMDA receptor antagonists have shown limited improvement in neuronal survival and in less injured regions after HI [16,17] and in the absence of thermoregulation, improved neuronal survival has been attributed to drug-induced hypothermia[18–20]. A recent clinical trial of xenon, a NMDA receptor antagonist in combination with cooling was also disappointing; though a delay in initiating therapy may have contributed to the lack of efficacy[21].

### *Magnesium and Inflammation*

Inflammation and infection have been implicated in neuronal injury. Magnesium sulfate may confer neuroprotection through down regulation of the inflammatory cascade. Magnesium significantly decreased the frequency of maternal and neonatal monocytes producing TNF- $\alpha$  and IL-6 when exposed to LPS in vitro[22]. Pre-clinical data have also demonstrated that magnesium reduces levels of pro-inflammatory cytokines (IL-6, TNF- $\alpha$ )[23] in LPS treated pregnant rodents as well as improves the offspring's learning ability at 3 months[24].

A potential anti-inflammatory mechanism is the inhibition of the Nuclear Factor- $\kappa$ B (NF- $\kappa$ B) signal pathway. NF- $\kappa$ B is a transcription factor present in cell cytoplasm and rapidly activated by inflammatory or immunological stimuli. On

activation, NF- $\kappa$ B enters the nucleus and initiates transcription of multiple genes to produce pro-inflammatory cytokines, cell adhesion molecules as well as regulators of apoptosis[25]. Gao and colleagues (2013) demonstrated that magnesium sulfate significantly reduces NF- $\kappa$ B activity by inhibiting its translocation into the nucleus in LPS sensitized adult rodent microglia[26].

In the preterm infants, inflammation may be an important etiological factor of brain injury. The risk of cerebral palsy in preterm infants increases in the presence of chorioamnionitis (OR 4.2, CI 1.4-12), prolonged rupture of membranes (OR 2.3, CI 1.2-4.2) and maternal infection (OR 2.3, CI 1.2-4.5)[27]. Preterm labor itself may have an underlying infective origin as demonstrated by raised pro-inflammatory cytokines in cord blood (IL-1, IL-6, IL-8 and TNF- $\alpha$ ). Maternal infection also increases the risk of cerebral palsy in term infants (OR 9.3, CI 3.7-23), especially if combined with perinatal hypoxia ischemia[28].

The theory that magnesium attenuates infective or inflammatory processes however has yet to be borne out in clinical trials. Subgroup analysis of the NICHD cohort receiving antenatal magnesium for the prevention of cerebral palsy demonstrated no benefit among infants exposed to chorioamnionitis[29].

## **ANIMAL MODELS OF NEUROPROTECTION**

Animal models of hypoxia ischemia have been used to assess the neuroprotective potential of novel therapeutic strategies. The Rice Vannucci rodent is one of the most commonly used animal models of hypoxia ischemia, combining unilateral carotid artery ligation with moderate hypoxia to generate cerebral injury[30]. Most studies using this method measure infarct area or volume and histological assessment of neuronal apoptosis to measure outcomes. Magnesium efficacy trials from term equivalent animals (postnatal day 7) have generated conflicting results[18]. Studies demonstrating neuroprotection were confounded by co-existing hypothermia and those that maintained normothermia failed to show benefit.

Large animal models provide an opportunity for more translational and clinically relevant outcomes. Magnesium failed to demonstrate a reduction in the level of secondary energy failure on magnetic resonance imaging[31] or severity of tissue damage in a piglet model of hypoxia ischemia[32]. In addition, magnesium sulfate has not demonstrated improvement of EEG or neuronal loss in fetal sheep undergoing umbilical cord occlusion at human term equivalent age (0.85 gestational age)[33].

Magnesium has also been evaluated in [adult](#) pre-clinical models of traumatic brain injury. Animals injured by fluid percussion to exposed dura (parasagittal) were treated with magnesium sulfate. Although there was no benefit observed in post-traumatic learning, there was a significant reduction in tissue loss in the hippocampus[34]. Similarly, magnesium significantly improved motor outcomes in rodents following diffuse axonal brain injury[35].

Animal studies of magnesium in fetal neuroprotection are limited compared to models of neonatal hypoxia ischemia. Timed-pregnant rodents have been used as a model of maternal infection to evaluate the role of magnesium in modulating inflammation to improve developmental outcomes in offspring[23,24].

[Temperature controlled studies by Galinsky and colleagues\[36,37\]](#) assessed the efficacy of magnesium sulfate given 24 hours prior to umbilical cord occlusion and maintained the infusion for a further 24 hours after insult in [preterm fetal sheep at 104 days gestation \(term is 147 days\)](#). Magnesium did not affect the cardiovascular response (degree of hypotension) during umbilical cord occlusion and thus did not alter insult severity. Although magnesium sulfate significantly reduced the frequency of seizures post-asphyxia, it did not improve EEG recovery or survival of subcortical neurons[36]. Magnesium was in fact associated with a reduction in mature (olig-2 +ve) oligodendrocytes in the intragyral and periventricular white matter and immature (CNPase +ve) oligodendrocytes in the intragyral region. The mechanism of this loss is unclear. The authors postulate that prolonged magnesium NMDA blockade may

interrupt neuronal-oligodendrocyte signaling and thus hinder oligodendrocyte differentiation and axonal myelination. Microglial infiltration did not differ between magnesium and control groups, suggesting that magnesium did not suppress inflammation in the 72 hours following hypoxia ischaemia[36].

## **NEUROPROTECTION STUDIES**

### *Neonatal Encephalopathy in Term infants*

Therapeutic hypothermia has been successfully implemented as a neuroprotective strategy in 2010 (NICE)[38], however in spite of this, 50% of newborns with moderate to severe HIE will die or suffer long-term disabilities such as cerebral palsy[39]. Therefore there is an urgent need to continue to develop new strategies to improve the care of this vulnerable population.

Magnesium inhibition of excessive NMDA receptor activation provides a biologically plausible mechanism to limit the delayed “secondary” phase of neuronal cell death following perinatal hypoxia ischemia. Interestingly, low magnesium levels at birth have been observed in infants with severe HIE (0.64mmol/L, 0.47–0.87) compared to mild or no HIE (0.81 mol/L, 95% CI 0.75-0.87) and controls (0.72 mmol/L, 95% CI 0.69–0.76)[40]. It remains unclear whether low magnesium at birth is a result of severe hypoxia or whether it confers vulnerability rendering infant susceptible to greater injury.

A pharmacokinetic study of magnesium by Levene and colleagues (1995) demonstrated doses of 250mg/kg MgSO<sub>4</sub> were not associated with significant hypotension or bradycardias in term infants following perinatal hypoxia ischemia[41]. The subsequent randomized asphyxia trial (RAST) however was suspended following incidences of significant bradycardia, which transpired to be the result of infants inadvertently receiving almost twice the intended trial dose. The pharmacokinetic study had used a 12.5% solution of magnesium sulfate, based upon the heptahydrated magnesium salt (MgSO<sub>4</sub>.7H<sub>2</sub>O). The pharmaceutical company, commissioned to supply the RAST with a 12.5% trial



medication, however provided a 12.5% solution based on the anhydrated salt (MgSO<sub>4</sub>); this solution was effectively double the intended concentration and therefore almost double the dose of magnesium was administered[42]. RAST recruited 50 patients prior to suspension (25% of the planned cohort) and no significant differences were found in mortality between groups. There was a trend towards higher mortality in infants given magnesium, although there was a disproportionately high number of infants with severe HIE in that group (unpublished data; communication with trial investigator D. Evans)

There have since been 6 randomized placebo-controlled trials assessing the use of magnesium sulfate in term hypoxia ischemia; 5 of which were conducted prior to the introduction of therapeutic hypothermia. These trials included infants born at least 35 weeks gestation with signs of moderate to severe encephalopathy (see table 2). There was however significant heterogeneity between trials in drug dosing and timing as well as outcome measures. All trials reported giving magnesium within 24 hours of birth, however only three stated this was within 6 hours[43,44]. One study protocol gave a single 250mg/kg dose of MgSO<sub>4</sub>[45] while others opted for an initial dose of 250mg/kg followed by repeat doses of either 125mg/kg[33,44] or 250mg/kg[43,46,47] at 24 and 48 hours. Bhat (2009)[43] and Ichiba (2002)[46] reported favorable-term composite outcomes; defined by a normal neurological exam at discharge, normal CT brain and normal oral feeding by 2 weeks. These findings however did not translate to significant neurodevelopmental improvement at 6 months[44] and 2 years[33].

Kashiba and colleagues adopted a novel approach, assessing the levels of excitatory amino acids (glutamate, aspartate) in the CSF at birth and 72 hours[45]. They noted higher levels of glutamate and aspartate in infants with more severe hypoxia ischemia, supporting the theory that secondary energy failure was the result of excitotoxic damage. Magnesium therapy however did not alter the levels of these amino acids.

Rahman et al (2015)[47] evaluated the safety and efficacy of magnesium combined with cooling following supportive evidence from adult rodent studies

[48–50]. They reported a favorable safety profile of magnesium sulfate administered during therapeutic hypothermia with no significant difference in death or hypotension between treatment groups. The study however had several methodological limitations; hypotension was defined as either mild-moderate (single inotrope) or severe (multiple inotropes) rather than specifying inotrope doses or mean arterial BP values; inclusion criteria varied between centers depending on the availability of aEEG; and 5/60 infants included in analysis underwent selective head cooling rather than total body hypothermia. Long-term outcomes for this study have yet to be published.

A comprehensive meta-analysis by Tagin and colleagues (2013) demonstrated a significant reduction in short term composite of 'unfavorable' outcomes, defined by abnormal neurology, aEEG or neuroimaging (RR 0.48, 95% CI 0.30-0.77)[51]. Ichiba and colleagues repeated their study in 30 newborns with moderate to severe HIE (based on Sarnat criteria) and administered MgSO<sub>4</sub> within 6 hours of birth[52]. They reported normal neuro-developmental outcomes in 73% infants at 18 months, though the study was limited by the absence of a control arm. There may be some benefit in the use of magnesium in term infants with HIE, however studies are limited by small numbers, trial heterogeneity and an absence of long term outcome data.

### *Fetal Neuroprotection*

Magnesium Sulfate (MgSO<sub>4</sub>) is a familiar drug in obstetrics and has been used in the management of eclamptic seizures since the early 1900s. Randomized controlled trials have since demonstrated its superiority over other anticonvulsants and it is currently recommended in the treatment of eclamptic seizures as well as seizure prophylaxis[3]. The neuroprotective properties of magnesium in preterm infants was first observed by Nelson and Grether (1995) who observed that in-utero exposure to MgSO<sub>4</sub> for pre-eclampsia or tocolysis was lower in very low birth weight infants (<1500g) with cerebral palsy compared to controls (7.1% vs 36%)[53]. While this promising finding was corroborating by some[54], the results proved controversial with other reports

failing to show benefit[55,56] as well as concerns of increased mortality in extreme preterm infants exposed to magnesium tocolysis[57].

Over the last decade, a number of large prospective randomized controlled trials have been conducted to assess the safety and efficacy of MgSO<sub>4</sub> as a fetal neuroprotective agent (see table 1).

In the Magnesium Endpoint Trial (MagNET 2002)[58], women in preterm labor were recruited between 24 to 34 weeks gestational age. They were stratified into two groups, those suitable for tocolysis (cervical dilatation < 4cm) and those who did not meet tocolysis criteria. The 'tocolysis' group was randomized to receive MgSO<sub>4</sub> (4g bolus and 2-3g/h infusion) or alternative therapy as deemed by the obstetrician. The other 'neuroprotective' group was randomized to MgSO<sub>4</sub> bolus (4g) or 0.9% Saline. The study however was stopped prematurely due to concerns of higher neonatal mortality rate in the magnesium group. Combined analysis of the trial arms did not demonstrate any reduction in cerebral palsy.

Two subsequent trials, the Australasian Collaborative Trial of Magnesium Sulfate (ACTOMgSO<sub>4</sub>)[59] study in 2003 and French PREMAG[60] Study in 2007 did not demonstrate an increased mortality with magnesium use. Neither trial however yielded significant improvements in rates of cerebral palsy at 2 years. The ACTOMgSO<sub>4</sub> trial did report a reduced rate of substantial motor dysfunction, as defined by a Gross Motor Function Classification (GMFCS) level of 2 or worse.

The Beneficial Effects of Antenatal Magnesium Sulfate (BEAM)[61] study in 2008 was one of the largest randomized controlled trials of magnesium involving 2241 women (singletons or twins) at 24 to 31 weeks gestation. This study demonstrated a significant reduction in moderate to severe (GMFCS 2-4) cerebral palsy as well as cerebral palsy overall. In addition to these four trials, the MAGPIE trial (2002)[62] was designed to assess whether magnesium prevented eclampsia in women with pre-eclampsia. Many of the participating centres were in developing countries and reported comparatively higher

pediatric mortality compared to other studies. There was no significant reduction in the rates of cerebral palsy associated with antenatal magnesium exposure.

Comprehensive meta-analysis of these five trials demonstrated antenatal magnesium sulfate reduced both the risk of cerebral palsy (RR 0.69, CI 0.54-0.87) and substantial gross motor dysfunction (RR 0.61, CI 0.44-0.85). The number women needed to treat to prevent one infant developing cerebral palsy was 63[63].

Outcome data at school age (6-11 years) however was disappointing. The ACTOMgSO<sub>4</sub> trial followed up 77% of their cohort and found no significant difference in cognitive, academic, attention or behavioral outcomes. The earlier finding of reduced gross motor dysfunction did not translate to an overall reduction in the severity of cerebral palsy at school age[64]. Long term follow up data from the PREMAG cohort (7-14 years) also reported no significant difference in neuromotor, cognitive or language ability. They did observe fewer incidences of grade repetition, specific educational needs and overall better parental perception of child health[65].

To date, there have been at least **five** meta-analyses[63,66–69] and an evaluation of cost effectiveness[70] that all support the use of antenatal magnesium sulfate as a neuroprotective agent. Clinical adoption of this intervention was initially slow with concerns raised over the lack of a statistical difference in primary outcomes as well as safety data raised in one trial[71]. The American College of Obstetricians has supported the use of magnesium in preterm neuroprotection, however encourages clinicians to develop guidelines locally[72]. Both Australia[73] and Canada[74] issued guidelines detailing the use of magnesium sulfate as neuroprotection of fetuses born less than 30 weeks and 32 weeks, respectively. The National Institute of Clinical Excellence (NICE) have recently recommended using magnesium sulfate in mothers in preterm labor at gestational ages 24 – 29+6 weeks and considering it in those at gestational between 30 – 33+6 weeks[75].

Although the long term follow up data from ACTOMgSO4 and PREMAG are disappointing, the findings do not negate the reduction in cerebral palsy at 2 years seen across the 5 trials included in the meta-analysis. It does however highlight the need for ongoing long-term evaluation of this intervention.

### **Neonatal encephalopathy in preterm infants**

NE seen in term infants represents a distinct clinical entity to the more chronic evolving cerebral white matter injury associated with prematurity. The preterm brain is particularly vulnerable to injury due to highly active dendritic and axonal growth as well as the exaggerated inflammatory response of an immature immune system. Although hypoxic ischemic events may complicate preterm delivery, there is limited evidence that interventions trialed in term infants can be directly translated to the preterm population. A small pilot study of selective head cooling in infants between 32 – 35 weeks gestation was associated significant adverse effects[76]. Designing a randomized control trial to evaluate neuroprotective strategies in preterm infants with NE is challenging due to the relatively low incidence and difficulties in accurately identifying signs of encephalopathy.

### *Adult Neuroprotection*

In addition to the preterm and term infant populations, magnesium sulfate has been evaluated as a rescue therapy in adult neurological injuries. The proposed mechanism of benefit includes NMDA blockade as well as dilatation of penetrating cerebral arterioles.

The Intravenous Magnesium Efficacy in Stroke[77] (IMAGES) trial was a large double-blind randomized control trial assessing the benefit of magnesium sulfate in acute ischemic strokes. The trial recruited 2368 participants with a clinical diagnosis of stroke, aiming to start magnesium or placebo within 12 hours of the onset of symptoms. Disappointingly, magnesium did not affect the primary outcome of death or disability at 90 days post-event. There was

however a significant improvement in a subgroup of patients with lacunar infarcts, mostly secondary to small cortical emboli.

The lack of efficacy in the IMAGES trial was thought to be a result of delayed magnesium therapy as only 3% of individuals received the drug within 3 hours of symptoms. This led to the novel approach of pre-hospital initiation of therapy pioneered in the Field Administration of Stroke Therapy–Magnesium (FAST-MAG) trial in 2004[78]. Saver and colleagues (2015) subsequently enrolled 1700 patients to receive magnesium or placebo within 2 hours of symptom onset[79]. Patients received a loading dose by paramedics and were started on a 24-hour magnesium infusion on arrival to hospital. Magnesium however was not shown to reduce death or level of disability at 90 days. The trial primarily involved acute ischemic strokes (73%) rather than intracranial hemorrhage (23%). Subgroup analysis of stroke type did not show any alteration of treatment effect.

Trials of hemorrhagic strokes have mostly focused on the use of magnesium in aneurysmal subarachnoid hemorrhage (SAH). Approximately a third of survivors deteriorate 3 – 14 days post-hemorrhage as a result of delayed cerebral ischemia. The underlying etiology of this process is likely multifactorial, including oxidative stress, vasoconstriction, inflammation and cortical spreading depression (CSD)[80]. Magnesium was not found to improve clinical outcomes after aneurysmal SAH in a large randomized control trial[81] and meta-analysis[82].

## **LIMITATIONS OF STUDIES**

Although the use of magnesium sulfate in fetal neuroprotection has shown promise in human clinical trials, results from neonatal and adult neurological injuries have been disappointing. There are a number of factors that may be contributing to this apparent lack of efficacy.

Magnesium levels in trials are usually measured in serum, which represent less than 1% of the total body content and do not accurately reflect intracellular levels[4]. Using serum levels alone to define a neuroprotective concentration may be insufficient if the neuroprotective mechanism is through intracellular anti-inflammatory mechanisms in addition to synaptic NMDA receptor blockade.

Pre-clinical rodent data suggest a neuroprotective 'target serum level' of approximately 2 – 3 mmol/L[83,84] , noting cardiodepressive effects at higher concentrations[84]. However, in vitro studies on rodent hippocampal neurons have suggested magnesium concentrations 2–4 times normal serum levels may be necessary to achieve benefit[85,86]. Achieving at least double serum magnesium levels in the CSF may provide a challenge given the limited CSF penetration with peripherally infused magnesium. Pharmacokinetic data from adult neurosurgical studies demonstrated doubling plasma magnesium resulted in only a modest 11-21% increase in CSF levels[87]. We have demonstrated similar findings in a piglet model of NE (fig3). Furthermore, CSF and serum magnesium levels do not correlate well following peripheral infusion. Levels in the serum rapidly rise within 30 minutes and then fall, whereas it takes 90 minutes before a significant rise is detected in the CSF[88].

The adage 'time is brain' is a key principle underpinning successful neuroprotective strategies. Developing a delivery mechanism to achieve a 'neuroprotective' magnesium concentration in the CSF whilst avoiding the toxicity associated with high serum levels represents a major challenge.

## Conclusion

Magnesium sulfate could be considered as an added adjunct to hypothermia with its inherent advantages of widespread availability, low cost and good

**safety profile.** It has been extensively evaluated in a number of different neurological disorders across all age groups from the preterm to the elderly. Evidence of benefit appears most convincing in fetal neuroprotection, possibly due to the increased susceptibility of the immature brain to excitotoxicity and increased infective and inflammatory risks associated with prematurity.

The use of magnesium sulfate in term NE however remains controversial. Early trials of magnesium in term infants with perinatal asphyxia were limited by small numbers, methodological heterogeneity and mostly pre-dated the widespread implementation of therapeutic hypothermia. In the post-cooling era, neuroprotective interventions are likely to take the form of adjuncts to incrementally improve outcomes beyond those achievable by hypothermia alone. Magnesium has been shown to augment therapeutic hypothermia in adult rodent models, however caution is warranted given possible adverse effects on neuronal cell architecture. Further pre-clinical evaluation is essential to ensure safety and efficacy of magnesium neuroprotection prior to further human clinical trials.

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