ROLE OF MAGNESIUM SULPHATE FOR NEUROPROTECTION IN PRETERM LABOR: SIMPLE REVIEW ARTICLE

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Abstract

Preventing neurologic impairment linked to premature delivery is a significant obstacle in the field of perinatal medicine today. The main topic of this review, magnesium sulfate (MgSO4), has been suggested as a significant advancement in that regard. MgSO4 is inexpensive, readily available, and has been suggested as an essential component of the care of unavoidably premature birth. Numerous systematic reviews have examined the outcomes of the numerous RCTs on the use of MgSO4 for neuroprotection; other studies have concentrated on dosage regimens and side effects; very few have examined the mechanism of action of magnesium. As for managing the unavoidable preterm birth, numerous guidelines globally have highlighted MgSO4 as a crucial component of daily best practice due to its demonstrated ability to lower the likelihood of severe neurologic deficiency, specifically cerebral palsy, in individuals who are correctly selected. The benefits of using antenatal MgSO4 increase with increasing prematureness. We concluded that prenatal MgSO4 is safe and effective in preventing cerebral palsy in premature infants, according to several recent studies. It is thought to be efficient without sacrificing security. It should be mentioned that research is now being done on other neuroprotective substances, such as melatonin. The significant advantages of delaying cord clamping should not be overlooked by clinicians, especially in cases of premature birth.

Keywords; MgSO4; Fetal; Neuroprotection; Preterm labor.

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1. Introduction

Brain damage is a significant clinical issue that contributes to neurological morbidity and mortality in preterm newborns [1, 2]. The risk of neurodevelopmental disability is inversely correlated with gestational age at birth [3]. Over 30% of infants born preterm (less than 28 weeks gestation) will experience CP, cognitive impairment, or behavioral abnormalities, including autism spectrum disorders and ADHD [4, 5]. As a result, creating novel treatments and preventative measures is essential.

Encephalopathy of prematurity, or preterm brain injury in humans, comprised of two main conditions: impairment of brain development affecting both grey and white matter as well as neuronal connectivity, and overt brain injury frequently combined with periventricular/intraventricular hemorrhage (PVH/IVH), which occurs preferentially in white matter (also referred to as periventricular leukomalacia, or PVL) [6, 7].

The cause of brain lesions in preterm newborns is complex and partially understood, although it most likely involves inflammation or infection, hypoxia, hyperoxia, ischemia, excitotoxicity, and damage brought on by IVH or PVH [8]. The administration of magnesium sulphate (MgSO4) antenatally (as a preventive measure against preterm labor or as a prophylactic measure against seizures in preeclampsia) has been demonstrated to have neuroprotective effects [9]. Clinical cohort studies have also demonstrated a decreased incidence of both cerebral palsy (CP) and intraventricular/periventricular hemorrhage in the offspring of mothers who received this treatment [10].

2. Neurodevelopmental outcomes of preterm infants

2.1 Mental health/ behavioral problems

Compared to full-term newborns, preterm infants have been reported to have a higher chance of emotional problems such as melancholy and anxiety, ASD, avoidant personality, anti-social personality, and the inattentive subtype of ADHD [11]. Other research, particularly as these kids approach adolescence and adulthood, refutes this conclusion [12].

Johnson *et al.* examined the prognosis of psychiatric problems in EPI born in the United Kingdom and Ireland in 1995 at ages 2.5, 6, 11, 19, and 29 and compared it to that of term controls. After controlling for socioeconomic status (SES), those who had a psychiatric disorder at age 11 were more likely to experience mental health issues that lasted throughout adolescence. Researchers determined that childhood psychiatric disorders do not appear to persist into young adulthood for this population, despite the study showing that young adults who were born extremely preterm come up to have a greater incidence of anxiety, depression, and avoidant personality. However, there was no statistically significant difference between the preterm and term adults. One study weakness was the 42% of participants who were lost to follow-up in adulthood. These participants comprised a group of patients with lower IQs and SES and higher levels of cognitive impairment. As a result, the results can be biased and misrepresent the actual prevalence of mental illnesses in this adult group [12].

Utilizing the Modified Checklist for Autism in Toddlers (M-CHAT) survey, a Chinese version of the Gesell Development Diagnosis Scale (GDDS), the Sensory Integration Schedule (SIS), and neurological examinations, 102 LPI infants and 153 term infants born in China at 24 and 30 months of age were compared in this study. Babies without complex medical histories or newborn illnesses were chosen. In their study population of preterm children born without any serious issues, the researchers found that patients had a two to four times larger risk for ASD compared to their full-term peers. ASD was confirmed in 8% of the cohort sample [13].

2.2 Developmental delay

There is a higher chance of verbal, cognitive, sensory, and motor impairment in preterm newborns [10-13]. When children reach school age, these deficits can show up as behavioral issues or low academic performance [13, 14]. There are several variables that contribute to inferior neurodevelopment, including exposure to the environment, perinatal risk factors, and an immature brain. A meta-analysis came to the conclusion that over time, prenatal factors have less of an impact and environmental factors become more significant [11]. There is a correlation between a lower risk of developmental delay and greater GA and birth weight [11, 13]. Cognitive delay is less common in preterm infants exposed to magnesium or corticosteroids during pregnancy [15].

Low arterial pH of umbilical cord blood, low Apgar scores, IVH, chorioamnionitis, moderate-to-severe bronchopulmonary dysplasia (BPD), extended mechanical breathing, and seizures are perinatal variables that raise the risk of developmental delay [11, 14, 15]. There is a substantial correlation between IVH and PVL and reduced gross motor function [15, 16]. It has been discovered that

additional variables, including male sex, spoken languages other than English, black race, lower parental education, and SES, are linked to worse developmental outcomes [11-15]. The frequency of developmental delay in infants born in developing nations is higher than in industrialized nations, and this disparity in prevalence has been attributed to cultural differences, insufficient understanding, and resource scarcity [11]. When comparing LPI infants to full-term infants using corrected GA [14], there was no significant difference in the scores obtained using the Bayley-II scales of infant and toddler development. The study assessed patients using LPI infants at 12 and 18 months of age. Significantly lower scores were obtained using chronological age.

2.3 Neurosensory impairment

According to **Lin *et al.,*** the rates of bilateral blindness and severe hearing loss were 2.8% and 0.54%, respectively, at age 5 and 2.41% and 0.54%, respectively, at age 2. While developmental findings at 5 years were reported to be connected with more obstacles in later life, developmental findings at 2 years were found to be less predictive of later learning status [17]. The relationship between prenatal variables and neurosensory deficits such as cerebral palsy, blindness, and deafness was expounded upon by **Burnett *et al*.** Their results support those of **Lin *et al.*** in that severe visual and hearing impairments are comparatively uncommon in EPIs, with incidences of less than 3% and 2% in toddlers, respectively [17, 18].

3. MgSO4 for neuroprotection

The discovery that the rate of CP in preeclampsia was significantly lower than in gestationally age-matched normotensive pregnancies marked the beginning of the MgSO4 story for neuroprotection. After a number of theories were put up, the protective factor was ultimately thought to be prenatal MgSO4 consumption [19].

Crowther *et al.*'s Individual Participant Data (IPD) meta-analysis [18], which combined data from large trials (5493 women and 6131 newborns), found no discernible effect of MgSO4 therapy on the key outcome of baby mortality or CP. A notable decrease in the risk of mortality or cerebral palsy (CP) was observed when the meta-analysis was limited to the four trials where MgSO4 was administered for fetal neuroprotection (RR 0.86, 95%CI 0.75–0.99, 4448 newborns). There was no discernible impact on the probability of infant mortality overall, in relation to possible harm to the babies. Without posing a serious risk to the unborn child, this IPD meta-analysis suggests using prenatal magnesium in planned or anticipated preterm births for fetal neuroprotection [20].

4. Why magnesium, and how does it work?

Uncertainty surrounds the precise mode of action of prenatal magnesium solubility (MgSO4) in embryonic neuroprotection. The neuroprotective ability of MgSO4 to prevent early abnormal neuronal cell apoptosis [21, 22], to prevent the release of inflammatory and cytotoxic agents [23], to decrease neuroinflammation and increase seizure threshold [24], to decrease cerebellar hemorrhage [25], to stimulate local adaptation responses through vasodilatation and better cardiovascular responses generally [26], and to promote neurogenesis in premature brain cell maturation by stimulating the secretion of neurotrophic factors [27, 28] have been suggested as potential explanations for the neuroprotective effects of MgSO4.

Additionally, MgSO4 may control or enhance vascular tone, maintaining adequate oxygen delivery to organs in the process [29-31]. This supports the cardiovascular system's ability to compensate for hypoxia, protecting cells in several organs, particularly the brain [30]. The so-called brainsparing phenomenon protects the brain, heart, and adrenal glands preferentially by shifting blood [31]. It is yet unknown what biomolecular cascade MgSO4 uses to produce this specific protective action [31, 33]. The fetus exhibits improved vascular mapping and vascular flow, particularly in the pericallosal artery, following antenatal MgSO4 exposure, according to clinically relevant results from color flow mapping by prenatal ultrasound [34].

Preterm newborns must avoid cerebral hypoxia at all costs to prevent brain damage. Rather than increasing the delivery of oxygen, MgSO4 reduces the demand and consumption of oxygen, preventing oxygen shortage in the cellular brain. One significant way that MgSO4 may preserve the developing brain is by balancing the delivery and consumption of oxygen by reducing the demand for it [35].

Another mechanism of MgSO4 preservation of the preterm infant brain was hypothesized by **Koning *et al.*** Through the establishment of mitochondrial resistance and the mitigation of inflammation in the rat model, MgSO4 preconditions the preterm neonatal brain to withstand hypoxia-ischemia brain injury. Rats that were 7 days old were given a bolus of magnesium sulfate (MgSO4) between 6 and 12 hours prior to hypoxic-ischemic insult. By maintaining mitochondrial respiration and lowering the generation of ROS and inflammation, this intervention lessened brain damage [36].

5. MgSO4 administration

4.1 GA at which MgSO4 is given

In the 2009 Cochrane review, MgSO4 was administered to all women at <34 weeks of gestation, with 68% of them at <30 weeks. Because the absolute risk difference from therapy is expected to be bigger at earlier gestations, cerebral palsy is inversely correlated with gestational age. Consequently, at earlier gestational ages, the numbers needed to treat will be smaller; at later gestational ages, they will be higher [37, 38].

4.2 Optimal timing for MgSO4 adminstratation

MgSO4 was administered when delivery was anticipated or scheduled within a 24-hour period in two of the four trials that made up the Cochrane review [19]. These trials' subgroup analyses revealed an RR of 0.81 (0.68–0.97) for cerebral palsy or death [38]. In the MgSO4 group of these two trials, the median time from randomization to birth was between 1.6 and 3.7 hours.

Previous research has demonstrated that newborn magnesium sulfate concentrations remained increased for up to 24 hours and that prenatal infusion allows for the timely transmission of MgSO4 to the mother (within 30 minutes). This suggests that MgSO4 enters the fetus quickly after the infusion is started and crosses the placenta [38].

4.3 MgSO4 optimal regimen

The amount of MgSO4 used varied from study to study, with loading doses ranging from 4 to 6 g and inconsistent administration of a maintenance dose. A meta-analysis came to the conclusion that while the trials employing lower overall dosages of MgSO4 continued to show a favorable impact, there is presently not enough data to establish an ideal regimen for administration or a minimum effective dose. Serum magnesium monitoring is not generally advised, and magnesium toxicity is unlikely at the dosage suggested below [39].

4.4 MgSO4 adverse effects

When administered intravenously, magnesium sulfate causes flushing, sweating, and a feeling of warmth since it is a peripheral vasodilator. Other side effects associated with dosage and infusion speed that have been documented in mothers include headache, nausea, vomiting, palpitations, and, in rare cases, pulmonary edema. Adverse effects on the heart and nervous system can arise from overdosing. There is no proof that the newborn had any unanticipated negative effects. Although MgSO4 was once thought to be a tocolytic, there is no proof that using it causes a delay in delivery [40].

5. Conclusion

Prenatal MgSO4 has been shown to be safe and effective in preventing cerebral palsy in premature infants, according to a number of recent studies. It is thought to be efficient without sacrificing security. It should be mentioned that research is now being done on other neuroprotective substances, such as melatonin. The significant advantages of delaying cord clamping should not be overlooked by clinicians, especially in cases of premature birth**.**

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