The neuroprotective effects of magnesium sulfate in utero exposure

Teodor Salmen\textsuperscript{1}, Vlad Dima\textsuperscript{2}, Claudia Gabriela Potcovaru\textsuperscript{3}, Bianca Margareta Mihai\textsuperscript{4}, Delia Cinteza\textsuperscript{5}, Roxana-Elena Bohiltea\textsuperscript{2}

\textsuperscript{1}Doctoral School, “Carol Davila” University of Medicine and Pharmacy, “N. C. Paulescu” National Institute for Diabetes Mellitus, Nutrition and Metabolic Disorders, Bucharest, Romania
\textsuperscript{2}Department of Obstetrics, Gynecology and Neonatology, “Carol Davila” University of Medicine and Pharmacy, Filantropia Clinical Hospital, Bucharest, Romania
\textsuperscript{3}Doctoral School, “Carol Davila” University of Medicine and Pharmacy, National Institute of Rehabilitation, Physical Medicine and Balneoclimatology, Bucharest, Romania
\textsuperscript{4}Department of Obstetrics and Gynaecology of Filantropia Clinical Hospital, Bucharest, Romania
\textsuperscript{5}Department of Rehabilitation Medicine, “Carol Davila” University of Medicine and Pharmacy, National Institute of Rehabilitation, Physical Medicine and Balneoclimatology, Bucharest, Romania

ABSTRACT

Prematurity affects 1 in 10 births and is associated with different degrees of disability and leads to a higher risk of neurological impairment and cerebral palsy (CP). Because its prevalence increase, but with a decrease in mortality rate, there is a burden of survivors that develop sequelae, a problem for the healthcare systems worldwide and for the patient’s social integration. Magnesium sulfate is a useful tool to limit the development of such complications. The risk factors for preterm brain injury act antenatally, intrapartum and postpartum. Even though there are several trials that tried to assess it benefits, magnesium sulfate is on the D list of U.S. Food and Drug Administration for pregnancy and several Societies of Obstetrics and Gynecology tried to implement national guidelines for its safe use. In conclusion it should be used with caution, within 24 hours before birth and under medical surveillance and to administer it only in pregnancies that are at high risk of premature childbirth. If there is a medical emergency involving the mother or the fetus, delivery should not be postponed in order to administer de magnesium sulfate.

Keywords: prematurity, magnesium sulfate, brain injury, exposure, neuroprotection, dosage

INTRODUCTION

Prematurity is linked to a higher risk of neurological impairment and cerebral palsy (CP) that lead to different degrees of disability and its consequences, resulting in a serious health burden. Delivery occurring before 37 gestational weeks is a preterm birth and affects 1 in 10 births [1]. Between 1990 and 2010, the premature birth rate increased worldwide, but the mortality rates decreased. Despite the decline in the mortality rates, there is an increase in the number of survivors that develop sequelae, an important aspect being represented by the associated neurodevelopmental disability, respectively, severe motor disorders or CP, representing a high burden for the healthcare systems worldwide and a major problem for their social integration [2,3].

Potential risk factors cited as contributing to preterm brain injury are grouped in three categories, respectively:

- antenatal factors – chronic hypoxia or hypoxia-ischemia, asphyxia and infections;
- preterm birth itself and by its consequences – immature vasculature development, reduced antioxidant capacity or vulnerable pre-oligodendrocytes;
- postnatal factors – need of mechanical ventilation, anticonvulsants or corticosteroids, poor respiratory functions, hemodynamic instability or infections [3,4].

With a lifetime cost of 11.5 billion for those born in the United States in 2000, CP is one of the most common causes of juvenile physical disability [5]. It is critical to understand that neurodevelopmental
abnormalities are widespread in prematurely born infants, in order to minimize the prematurity impact as much as possible as well as to assist with the resource allocation. Preventive therapy options for preterm newborns in order to minimize brain injury are limited. The only prenatal neuroprotection clinically available, currently, are represented by corticosteroids and magnesium sulfate [2].

Magnesium sulfate represents a useful tool if used before an early preterm birth, consisting in the severity and incidence decrease of the leading cause of children’s neurologic impairment, respectively, of CP [6].

The mechanism involved in magnesium sulfate’s neuroprotection is not unveiled, but the hypothesis are that it acts through one or more of the following:

- antioxidant effect;
- stabilization of neuronal membranes, blocking excitatory neurotransmitter such as glutamate;
- anti-inflammatory effect;
- normalizing cerebral blood flow and stabilizing blood pressure [7].

In The MagNUM study, mothers at risk of preterm birth, with a gestational age between 30 and 34 weeks, were administered 4 grams of magnesium sulfate when the preterm birth was expected within a period of 24 hours and, later, the newborns underwent diffusion tensor MRI at the normal expected term of delivery. Antenatal magnesium sulfate intake did not promote the development of white matter microstructure in pathways impacting motor or cognitive function, so, if the neuroprotective benefit of magnesium sulfate treatment administered in preterm birth is verified, the mechanisms are unlikely to be related to the rapid white matter maturation estimated from fractional anisotropy [8].

Even though magnesium sulfate use in pregnancy is allowed, the U.S. Food and Drug Administration included it in the D category list, respectively, in the drug category that have evidence for human fetal risk, but that can be used limited because of their potential benefit and the recommendation is to be administered in the lowest dose and in the shortest possible duration, suggesting to be no longer than five to seven days [2,9].

The evidence about neuroprotection effects of magnesium sulfate comes from three randomized control trials and meta-analysis – Australasian Collaborative Trial of Magnesium Sulfate (ACTOMgSO4) [10], the Beneficial Effects of Antenatal Magnesium Sulfate (BEAM) trial [11], and the PREMAG trial [12], that are characterized by heterogeneity both in the material and methods, respectively usage of different dosing regimens, different gestational age at administration and, also, in the results regarding death, CP and gross motor dysfunction [6].

American College of Obstetrician and Gynecologists (ACOG) has not emitted a straight protocol, but they let the recommendation for its use as a neuroprotector, leaving each society to elaborate their guidelines, so several societies tried to implement guidelines, and the more frequent recommended dosage used was 4 grams bolus dose followed by 1 gram per hour up to 24 hours [2]. For example, Romanian’s Health Ministry and Romanian’s Society for Obstetricians and Gynecologists emitted a guideline that recommends administration of magnesium sulfate for neuroprotection in case of pregnancy urged to be delivered before or at 32 weeks of gestation, but under strict medical surveillance and in a dosage of 4 grams bolus followed by 1 gram per hour up to 24 hours or up until the delivery take place [13]. Canadian Society of Obstetrician and Gynecologist recommends its for imminent preterm birth (≤33 + 6 weeks) in a 4 grams intravenous loading dose, followed or not by 1 gram per hour maintenance infusion until birth [14]. Australian guidelines recommend administration of magnesium sulfate between 24 and 30 gestational weeks with 4 grams loading intravenously dose, followed by 1 gram per hour intravenous infusion [15].

It is important to establish the best candidates that can benefit from magnesium sulfate administration. Women who are at a high risk (recent preterm prelabour rupture of membranes, preterm labor with intact membranes, medically planned or obstetrically advised preterm cesarean delivery) of giving birth prematurely within the next 24 hours are suitable for magnesium sulfate neuroprotection medication.

The beneficial results depicted by the trials that included sulfate magnesium in preterm births are for:

- CP - a relative risk (RR) of 0.68 (95% CI 0.54-0.87), with an absolute risk reduction of 1.6%, with a number needed to treat (NNT) of 63 (95% CI 43-87) [16]
- gross motor dysfunction – a RR of 0.61 (95% CI 0.44-0.85) and a neuroprotection RR od 0.6 (95% CI 0.43-0.83) [17,18]
- death or CP – a RR of only 0.94 (95% CI 0.78-1.12), but with a RR of 0.85 (95% CI 0.74-0.98) in neuroprotection trials subgroup [17]
- stillbirth or pediatric death – the reduction was not significant, with a RR of 1.04 (95% CI 0.92-1.17) and, respectively, of 0.95 (95% CI 0.8-1.12) in neuroprotection trials [18].

There are several precautions and contraindications in using this therapy. In myasthenia gravis the administration of magnesium sulfate is strongly contraindicated because it slows down already inhibited nerves-muscle connections [19]. In patients with myocardial compromise, cardiac conduction defects or with impaired renal function magnesium sulfate
should be used with caution because of its inotropic negative effects and renal elimination.

Although magnesium sulfate therapy for neuro-protection has not been studied in women who are pregnant for fewer than 24 weeks, a prospective trial looking at the effectiveness of magnesium sulfate in combination with corticosteroids in women who are 22 to 26 weeks pregnant is currently undergoing. Compared to preterm infants who solely received corticosteroid therapy as a treatment, preterm infants who received both corticotherapy and magnesium sulfate had a lower rate of impairment and death [20].

The dosage and rate of administration varies, but the most common is 4 grams intravenously in 20 minutes followed by a 1 gram per hour maintenance dose. Higher doses (6 grams loading, 2 gram per hour maintenance) are not safe enough because magnesium sulfate may have both neuroprotective and toxic fetal effects depending on dose.

The proper administration of magnesium sulfate is within 24 hours before birth with several cautions. It is important to reserve this therapy only for those women who are at high risk of premature childbirth. When we give magnesium sulfate to a woman who is scheduled for a cesarean birth, the goal is to give her 6 to 12 hours of maintenance therapy before the procedure. If there is a medical emergency involving the mother or the fetus, delivery should not be postponed in order to administer magnesium sulfate. If we predict that the labor will take longer than 24 hours, then the administration of magnesium sulfate should be delayed.

Even though there are new data regarding magnesium sulfate and because it is part of numerous national guidelines including in the Romanian one, its use will be preserved in the next year update of the guideline, the next step that should be implemented is that each hospital to develop internal guidelines for its use.

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