Gineco.eu[12] 36-38 [2016]
DOI: 10.18643/gieu.2016.36

Fetal neuroprotective role of magnesium sulphate

Iulia Tarcomnicu[1], M. Dimitriu[1], Liana Ples[2], M. Banacu[1], Alina Calin[3], Ana Nastas[1], Dan Navolan[4], Nicolae Bacalbasa[5], Cringu Ionescu[1]

1. "Carol Davila" University of Medicine and Pharmacy, Department of Obstetrics and Gynecology, "St. Pantelimon" Clinical Emergency Hospital, Bucharest, Romania
2. UMF "Carol Davila" University of Medicine and Pharmacy, Department of Obstetrics and Gynecology, "St. Ioan" Clinical Hospital, Bucharest, Romania
3. UMF Department of Obstetrics and Gynecology, Galati, Romania
4. Department of Obstetrics-Gynecology, "Victor Babes" University of Medicine and Pharmacy Timisoara, Romania
5. "Carol Davila" University of Medicine and Pharmacy, Bucharest, Romania

Correspondence:
Dr. Cringu Ionescu
e-mail: antoniuginec@yahoo.com

Abstract

Magnesium sulphate ($MgSO_4$) is used for very long time in Oobstetrics as anticonvulsivant, antihypertensive and tocolytic and in pediatrics as anticonvulsivant, anti-anaphylactic and antispasmodic. In recent years we have found that the use of antenatal $MgSO_4$ to women with imminence of premature birth may have fetal neuroprotective role. Babies born too early have a higher risk of dying in the first weeks of life than babies born at term, and those who survive often have damage in the form of cerebral palsy, blindness, deafness or physical disabilities. Neonatal morbidity and mortality rates attributed to prematurity, increase proportionally with the lower the gestational age is at the moment of birth. In the mid 1990s, observational studies suggests that premature infants born by mothers who received $MgSO_4$ as tocolytic or for other obstetrical indications had a lower rate of cerebral palsy compared to children born prematurely by women who haven't been exposed to therapy with $MgSO_4$. The objective of this review is to analyze the results of randomized, controlled studies which investigates the neuroprotective effect of $MgSO_4$ against to specific neurological disease of prematurity.
Keywords: *premature newborn, magnesium sulfate, fetal neuroprotector, cerebral palcy*

Introduction

The frequency of premature birth worldwide has reached 5-10% in recent years and does not tend to fall, continued to be one of the greatest challenges of perinatal medicine. Premature birth is one of the most important causes of perinatal morbidity and mortality, producing 50% of neonatal deaths, 70-80% of neonatal early deaths and 65-75% of infant mortality[1]. In these cases neonatal mortality occur 8-13 times more frequently than those carried to term.

The main risk factor for neurological damage are premature births (gestational age less than 34 weeks) and very low birth weight (less than 1500 g), causes that are responsible for approximately 17-32% of cases of neurological impairment in children[2]. Due to introduction of modern methods of care offered to premature newborns, death of children with weight between 1000-1500 g decreased from 50% to 5%, while those weighing between 500 and 1000 g from 90% to 20%. Premature babies born at 23-27 weeks which survive, have a risk 80 times more likely to develop cerebral palsy than babies born at term[3,4].

Currently are implemented protocols for the conduct of premature birth, which unfortunately does not contain any information about the possibility to prevent or reduce the frequency and severity of cerebral palsy in newborns.

In this review we analyzed the results of several studies in regards to the recommendations on the management of the premature birth, which took into consideration the possibility of reducing the risk of cerebral palsy in newborns through the use of magnesium sulphate ($MgSO_4$). The mechanism of its neuroprotective effect was not fully studied, but may experience due to the antioxidant effect, reducing the production of proinflammatory cytokines, blocking glutamate-activated calcium channel, stabilize cell membranes, improve cerebral blood flow and prevent low blood pressure in newborns[5].

The confidence of the neuroprotective effect of $MgSO_4$ is based on data from observational studies, randomized controlled trials and meta-analyses.

The first study about a possible beneficial effect of $MgSO_4$ in reducing the risk of cerebral palsy in newborns, was published in 1995. This observational study conducted by Nelson and Grether analyzed the consequences of premature birth to children with very low birth weight. They concluded that in cases where the mother received therapy with $MgSO_4$ (as tocolytic, or for other obstetric indications), the frequency of cerebral palsy in infants was significantly lower than in group of mothers who were not treated with $MgSO_4$[6]. The authors of the study were those who showed antenatal $MgSO_4$ administration as a major breakthrough. After the publication of this data by Nelson and Grether were conducted randomized controlled trials concerning this therapeutic principle[6-8].

Randomized Controlled Trials

We analyzed the results of several randomized controlled trials: The Australasian Collaborative Trial of magnesium sulphate collaborative group (ACTO $MgSO_4$), Beneficial effects of antenatal $MgSO_4$ (BEAM), $MgSO_4$ Given Before very-preterm birth to protect infant brain (PREMAG), as well as the results of other studies in order to bring new information about $MgSO_4$ as neuroprotective and providing the usefulness in current practice (Table 1).

BEAM - is a randomized clinical trial that was conducted at the National Institute of Neurological Disorders and Stroke and the National Institute of Child Health and Human Development, Eunice Kennedy Shriver[8]. The study included 2136 women between 24.0 and 31.6 weeks of gestation with imminence of premature birth

Received:
October 11, 2015
Revised:
November 28, 2015
Accepted:
January 04, 2016

(i.e. birth to be completed between 3 and 24 hours). The women were divided in two groups. The first group received $MgSO_4$ in a dose of 6 g, followed by infusion of 2 g/h. In the second group was used placebo. If during 12 hours the birth does not occur the treatment is stopped. The main result of the study showed about the same results for the perinatal mortality rate in both groups (11.3 vs. 11.7%, RR 0.97, CI 0.77 to 1.23 95%), but the incidence of severe forms of infant cerebral palsy was significantly lower in the group of patients treated with MgSO4 (1.9 vs. 3.5%; RR 0.55; 95%, CI 0.32 to 0.95). A further division in periods of the gestational age <28 and ≥28 weeks led to the conclusion that the use of magnesium in the lower age lead to a significant reduction in the incidence of cerebral palsy. The risk of death was about the same in both groups (9.5 vs. 8.5%, RR 1.12; 95% CI 0.85 to 1.47).

PREMAG - a randomized study that examines the use of $MgSO_4$ preparations as neuroprotective. It is a study that included 573 women under 33 weeks of pregnancy[5]. Women were randomly assigned into 2 groups. The $MgSO_4$ was administered in the first group, at a dose of 4 g of $MgSO_4$ in 40 ml isotonic saline (0.9%), administered for 30 minutes without further additional administration and the second group was the placebo. The children were followed for two years after discharge from hospital. The study shows the protective effect of $MgSO_4$ on the development of severe forms of cerebral palsy (10.0 vs. 11.7%; 95% CI 0.42 to 1.03).

ACTO $MgSO_4$ - is an Australian study that evaluates the effectiveness of $MgSO_4$. This study included 1,062 women with age of gestation between 30 and 34 weeks, who were giving birth in the next 24 hours[7]. Patients were divided into two groups. In the first group $MgSO_4$ was administered intravenously 4 g of $MgSO_4$ and 50 ml isotonic solution of chloride of sodium (0.9%), the rate of infusion of 1 g/h, and in the second group the patients were perfused with 50 ml of solution sodium chloride 0.9% (placebo). Further infants were followed for two years and studied the incidence of infant mortality, cerebral palsy and other neurological abnormalities. The study reached the following conclusions.

In the group where was used $MgSO_4$, they found lower rates of infant mortality 13.8 vs. 17.1%; (RR: 0.83; 95% CI 0.64 to 1.09) the incidence of infantile cerebral palsy was 6, 8 vs. 8.2%; (RR: 0.83; 95% CI 0.54 to 1.27) and total mortality 19.8 vs. 24.0%, (RR: 0.83; 95% CI 0.66-1.03).

Children with cerebral palsy from magnesian therapy group had less severe motor disabilities (3.4 vs. 6.6%, RR: 0.51; 95% CI 0.29-0.91) and a lower incidence of mortality associated with them (compared to 17.0 22.7%; RR: 0.75; 95% CI 0.59-0.96).

Another study with the same purpose and principles, MAGENTA[9] is assessing the benefits of $MgSO_4$ as neuroprotective in women with imminence of premature birth and pregnancy age between 30 and 34 weeks. Patients included in the study were divided in two subgroups. Patients with magnesium sulfate group receives 50mL infusion containing 8 g $MgSO_4$, placebo group received 50 ml 0.9% sodium chloride isotonic solution, both administration being made in the course of 30 minutes. The children of these patients were followed for two years after birth. The study concluded that mortality and cerebral palsy among those who received antenatal $MgSO_4$ were 5.4% lower compared to the placebo group 9.6%[10].

A study performed in Texas in 20 maternity evaluated the effects on fetal middle cerebral artery (MCA) after administration of $MgSO_4$ antenatal on pregnant women with imminent premature birth[10]. In study were included 2241 pregnant women divided in two groups: placebo group and the group with the administration of $MgSO_4$. Doppler measurements on the MCA were performed prior and after treatment (four times at different intervals of time). Parameters studied included: average velocity, systolic pick velocity the diameter of vessels, and heart rate. Conclusions show that $MgSO_4$ had no significant effects on fetal cerebral blood flow analyzed using Doppler. The

Table 1 $MgSO_4$ vs. placebo: main disease (Cochrane Review)[11]

The main diseases	RR, 95% CI
Death or cerebral palsy	0.85, 0.74-0.98
Death (fetal or late)	0.95, 0.80-1.12
Cerebral palsy	0.71, 0.55-0.91
Any neurologic disease	1.03, 0.87-1.21
Death or major motor dysfunction	0.84, 0.71-1.00

only parameter of fetal blood flow that was significantly modified by $MgSO_4$ was heart rate. The significance of this change in heart rate and the neuroprotective effects of $MgSO_4$ is unknown.

World Health Organization (WHO) recommended the usage of $MgSO_4$ as neuroprotective in pregnant women with pregnancy age before 32 weeks, with the imminence of premature birth, the goal proved being the prevention of infant cerebral paralysis. The neuroprotective effect of $MgSO_4$ is best achieved by being used up to 24 hours before premature birth. WHO recommended three dosing regimens of $MgSO_4$. First regime is represented by initial 4 g i.v. for 20 minutes and 1 g/hour until delivery; second regime: 4 g i.v. for 30 minutes or 4 g i.v. bolus as single dose; third regime 6 g i.v. for 20-30 min and 2 g/hour maintenance dose until birth. There is a need for further research to establish whether repeated treatment with $MgSO_4$ for neuroprotection is appropriate[11].

Conclusions

$MgSO_4$ presents proven neuroprotective effect in pregnancy less than 30 weeks pregnancy with risk of premature birth. Summarizing the results of studies, if we start to use $MgSO_4$ as neuroprotection, we get less than 1 case with cerebral palsy on every 63 pregnant women. For pregnant women under 28 weeks of pregnancy to prevent 1 case of infant cerebral palsy, the treatment is required for less than 29 pregnant women. By using the$MgSO_4$ as neuroprotection it would result fewer infant cerebral paralysis, ultimately requiring financial resources far greater than the cost of antenatal treatment with $MgSO_4$, being a very good result cost-effective .

For the neurological effect of $MgSO_4$ treatment at 30-34 weeks it should be conducted more randomized trials. WHO 2015 recommended the usage of $MgSO_4$ as antenatal neuroprotection in pregnant women at risk of premature birth before 32-34 weeks of pregnancy. ■

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