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Procedures for fetal neuroprotection: use of magnesium sulfate

Procedimentos para neuroproteção fetal: uso do sulfato de magnésio

Editorial

Perinatal factors resulting from prematurity are the main agents responsible for high child morbidity and mortality worldwide[1]. Therefore, the impact of premature birth is currently one of the biggest obstetric challenges. Prematurity is classified as spontaneous or elective[2]. The spontaneous one is the result from spontaneous delivery labor in the strict sense of this term or from rupture of the membranes, and it occurs more frequently in multiple pregnancies. On the other hand, elective prematurity is a consequence of a medical indication due to maternal intercurrent events (hypertensive emergencies, diabetic decompensation or placental displacement, among others).

Extreme prematurity is the most feared condition, which results from deliveries at gestational ages of less than 32 weeks. Because prematurity may perform an irreversible neurological damage to the child, it has the capacity to cause a wide spectrum of diseases and permanent conditions, with varying degrees of impairment with regard to both neurological and psychomotor development[3].

Although use of magnesium sulfate to provide prophylaxis against eclampsia and inhibit preterm delivery labor is a well-established therapeutic approach, its use with the aim of fetal neuroprotection has been addressed only in more recent studies. Magnesium promotes cerebral vasodilatation, thereby it reduces the production of cytokines and free radicals and the entry of calcium into the intracellular medium, which minimizes cell injury and consequent death and optimizes the cerebral blood flow[4]. In 1995, a case-control study reported that sulfation in cases of extreme prematurity was probably associated with fetal neuroprotection effects[5]. Following this, other analyses were conducted on its applicability within obstetrics as a prevention for neurological lesions in extremely premature infants.

Since only some of the subsequent studies showed that magnesium sulfate had a neuroprotective effect[6,7], while others reported that this effect might not be sustainable[8-10], new randomized studies were developed.

A systematic review from the Cochrane Collaboration produced a meta-analysis of five randomized clinical trials that assessed the effect of neuroprotection provided through using magnesium sulfate in cases of prematurity[11]. This review showed that its use significantly reduced the risk of cerebral palsy, but did not increase fetal, neonatal, infant (up to two years of age) or maternal mortality. The dose used in the different studies ranged on average from

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Study carried out at the Fetal Medicine Program in the Obstetrics Department of Escola Paulista de Medicina, Universidade Federal de São Paulo – UNIFESP – São Paulo (SP), Brazil.
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4 to 6 g, administered intravenously, 20 to 30 minutes after the mother's eclamptic seizure. This included a maintenance dose of 1 to 2 g per hour, for around 12 to 24 hours[11]. From the systematic review, management protocols were determined, however they did not have any consensus regarding the dose and inclusion criteria for use of medication.

In 2010, the American College of Obstetricians and Gynecologists (ACOG)[12] formally stated its opinion, through a committee, that sulfation presented encouraging evidence with regard to neuroprotection. However, it was only in 2012 that ACOG determined the inclusion and exclusion criteria regarding sulfation for fetal neuroprotection[13]. This procedure is indicated for pregnant women with a gestational age of less than or equal to 31 weeks and 6 days, presenting a risk of delivery within the next 30 minutes to 24 hours, with either a single or a multiple pregnancy, and also in cases of delivery labor with dilatation of 4.0 to 8.0 cm or spontaneous membrane rupture, if this occurs after the gestational age of 22 weeks has been reached. Another inclusion criterion is that sulfate should be used in cases of elective prematurity, in which delivery is indicated within the next 24 hours (severe preeclampsia). The exclusion criteria include maternal contraindications and uncertainty regarding whether the intervention would bring real benefits to the fetus, although the latter criterion is not very clearly defined. This probably correlates with situations in which the fetus presents minimal chances of survival or the length of time for drug action would be insufficient, like deliveries that take place during the expulsive period.

Other guidelines have also been established, such as the one of the Society of Obstetricians and Gynaecologists of Canada (SOCG) in 2011, in which sulfation is indicated only for pregnant women of gestational age of more than 31 weeks and 6 days, when preterm delivery is imminent (i.e. the active phase of delivery labor, with dilatation greater than or equal to 4.0 cm, with or without membrane rupture, or in situations of elective prematurity)[14].

It needs to be borne in mind that use of magnesium sulfate is not risk-free for the mother, especially in the presence of toxicity signs from this drug. Facial rubor and flushes are acceptable sensations from its use, but continuous monitoring of maternal clinical parameters is needed in order to ensure safe use. The parameters to be monitored include the pulse (heart rate – HR), respiratory rate (RR), arterial blood pressure (BP), patellar reflex (PR), and urinary output (UO). This last parameter especially should be measured while use of this drug continues. The infusion should always be halted in the following situations: HR<12 respiratory movements per minute, absence of RR, hypotension and UO<100 mL over a four-hour period. In situations of intoxication due to magnesium sulfate, the antidote used is calcium gluconate, which should be always easily accessible, with a dose already prepared as soon as the seizure dose of sulfate has been administered in the same way as done in preeclampsia treatment[15].

The possibility of neuroprotection for full-term fetuses using sulfation has also been addressed, as seen in the Cochrane systematic review. However, this showed that there was insufficient evidence to state that its use was effective and safe[16].

Therefore, despite the divergences in the criteria related to the gestational age for indication, dosage and effects of magnesium sulfate on preterm gestation, it is clear that magnesium sulfate has an effect with regard to neurological protection, especially at early gestational ages (less than 32 weeks). For better definition of the eligibility of sulfation use for neuroprotection, further randomized studies should be encouraged.

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