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REVIEW

The use of intravenous magnesium in non-preeclamptic pregnant women: fetal/neonatal neuroprotection

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Abstract
Purpose To review the effect of intravenous magnesium in obstetrics on fetal/neonatal neuroprotection.
Methods A systematic review of published studies.
Results Five randomized trials and 4 meta-analyses have shown a significant 32 % reduction of cerebral palsy when administering magnesium sulfate in case of preterm delivery. The pathophysiologic mechanism is not fully unraveled: modulation of the inflammatory process, both in the mother and the fetus, and downregulation of neuronal stimulation seem to be involved. After long-term high-dose intravenous administration of magnesium, maternal and neonatal adverse effects such as maternal and neonatal hypotonia and osteoporosis and specific fetal/neonatal cerebral lesions have been described. In case of administration for less than 48 h at 1 g/h and a loading dose of 4 g, these toxic amounts are not achieved. American, Canadian and Australian guidelines recommend the use of intravenous magnesium in any threatening delivery at less than 32 weeks. The "number needed to treat" to avoid 1 cerebral palsy is between 15 and 35.
Conclusions Intravenous magnesium significantly reduces the risk for cerebral palsy in preterm birth. Open questions remain the optimal dosing schedule, whether or not repeating when delivery has been successfully postponed and a new episode of preterm labor occurs. Some concern has been raised on a too optimistic value for random error which might have led to over-optimistic conclusions in classic meta-analysis. Randomized trials comparing different doses and individual patient data meta-analysis might resolve these issues.

Keywords Preterm birth · Cerebral palsy · Magnesium · Neuroprotection

Introduction

Although after the introduction of antenatal steroids and postnatal use of surfactant neonatal survival after preterm birth has greatly improved, preterm babies are at risk for poor long-term outcome. One of the most daunting complications of preterm birth is cerebral palsy (CP). The prevalence of CP is estimated between 2 and 2.5 per 1,000 live born babies. The risk is inversely related with gestational age. A baby born at a gestational age below 28 weeks has 30–80 times higher risk to develop CP as compared to a term neonate [1]. In 1995 Nelson and Grether noted in a population-based case–control study that CP was less frequent in preterm babies who had been exposed to magnesium sulfate antenatally [2, 3]. Since then this effect has been studied in randomized controlled trials. Other studies have clearly demonstrated that magnesium sulfate is neither a tocolytic nor an anti-hypertensive drug [4].

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The purpose of this review is to evaluate the effect and side effects of antepartal intravenous magnesium given in women who do not suffer from pre-eclampsia and to provide a possible biological background for these effects.

Methods

A Medline and Medbase search was performed using as search terms "intravenous and magnesium and pregnancy", "intravenous and magnesium and preterm" and "intravenous and magnesium and fetus". Only randomized controlled trials and meta-analyses were looked for with fetal/neonatal neurological outcomes as primary or secondary end points.

Results

A total of 483 references were found (date of access 20 November 2013); after scrutinizing all titles and if available abstracts, four randomized controlled trials could be retained and four meta-analyses reporting on the effect of maternal magnesium sulfate on neonatal and fetal neuroprotection. An overview of the original studies and their results is given in Table 1 [5–9]. One other trial, the so-called Magpie trial, had as primary end point the prevention of eclampsia in case of pre-eclampsia; fetal and neonatal neuroprotection were only secondary end points [10, 11]. Cerebral palsy was not specifically noted in the Magpie trial. The BEAM trial also stratified according to whether the fetus had been previously exposed to magnesium sulfate and results were consistent demonstrating significantly less CP after repeated doses of magnesium sulfate [9].

These RCTs have been analyzed in four different meta-analyses [12–15]. Two of these meta-analyses have been published by the same authors and are considered double publication of the same content [12, 13]. Not all meta-analyses included all RCTs but they do all show more or less the same results.

At this moment an "individual participant data" analysis is being performed on the original data of the studies to detect possible other factors that could influence the neonatal outcomes such as the reason for preterm birth (infection, preterm rupture of the membranes, maternal disease, etc.), the impact of individual gestational age, dose and way of administration of magnesium sulfate by the Australian research Center for health of women (ARCH). Results are to be expected in 2014 [16].

The Magpie trial has not been included in Table 1 because, as already mentioned, neonatal neuroprotection was not a primary end point. A follow-up study including 2,895 children from the MAGPIE trial at the age of 18 months demonstrated no difference in mortality between the magnesium sulfate and placebo group and a non-significant trend to a lower neurosensory disability score in the magnesium group [10, 11].

The general conclusions in the meta-analyses are that in utero treatment by maternal administration of magnesium sulfate at a gestational age of less than 32–34 weeks does not significantly reduce the risk of fetal/neonatal death or CP (relative risk 0.92; 95 % confidence interval 0.83–1.03) [15]. On the other hand looking only at CP, the reduction is significant (relative risk 0.28; 95 % confidence interval 0.54–0.84). The risk of perinatal death is not increased (relative risk 1.01; 95 % confidence interval 0.89–1.14). These effects become more obvious at a gestational age less than 30 weeks.

A more recent meta-analysis tried to evaluate the effect of magnesium sulfate on fetal neuroprotection for term pregnancies: the author concluded that it was not possible to find any study published looking at the outcome "fetal neuroprotection" or "cerebral palsy" in term pregnancies [17].

The Australian research center for health of women (ARCH) has started the MAGENTA trial to specifically look at the neuroprotective effect of magnesium between

Table 1 Original randomized studies on magnesium and fetal/neonatal neuroprotetcion with dosage and major outcome measures

Trial/acronym	Dose	Cerebral palsy RR (95 % CI)	Mortality RR (95 % CI)
Mittendorf/MagNET 2002; $n = 57$ [5] (neuroprophylaxis arm only)	4 g (bolus, no maintenance dose)	6.77 (0.37–125.65)	1.93 (0.19–20.18)
Marret/PREMAG 2006; ($n = 573$) [6, 7]	4 g (bolus, no maintenance dose)	1.37 (0.18–10.70)	0.88 (0.57–1.35)
Crowther/ACTOMgSO4, 2003 ($n = 1{,}062$) [8]	4 g (over 20 min) plus 1 g/h maintenance	0.85 (0.55–1.31)	0.81 (0.62–1.05)
Rouse/BEAM 2008 ($n = 2{,}441$) [9]	6 g (over 20–30 min) plus 2 g/h maintenance dose	0.59 (0.40–0.85)*	1.13 (0.87–1.48)

* Statistically significant in the advantage of magnesium/RR: relative risk

30 and 34 weeks of gestational age, and data have not yet been published [18].

There are of course many confounding factors modulating the effect of magnesium sulfate on CP. One relevant factor is gestational age and the effect is inversely related to gestational age. The different RCTs have different inclusion criteria including gestational age less than 32 weeks to less than 34 weeks at the moment of randomization. Cahill et al. [19] calculated that the number needed to treat was only 15 at the gestational age between 22 and 27 weeks and increased to 35 between 28 and 31 weeks to reach 336 between 32 and 36 weeks. As already mentioned in term children it is not yet possible to calculate this due to lack of data [17].

In analogy to the administration of corticosteroids in case of preterm labor, the influence of the interval between administration and timing of birth has been studied. Different RCTs have used very different protocols from administration as soon as birth is to be expected within 24 h to only when dilation has evolved between 4 and 8 cm without any further specification. Magnesium sulfate administered intravenously to the mother has been shown to be present in fetal serum 1 h after administration. A minimal administration time of 4 h seems to lead to the best results [20]. The dosing scheme was quite different in all studies and is summarized in Table 1.

At this moment the available data do not allow direct comparison between the different dosing schemes. The largest effect has been noted in the largest trial that also used the highest dose of magnesium sulfate being 6 g over 20–30 min followed by 2 g/h [21, 22]. The very recently published IRIS trial (different Infusion Rates of magnesium sulfate before preterm birth for neuroprotection trial) could only conclude that administering 4 g magnesium sulfate over 60 min did not result in a significant lower occurrence of maternal adverse effects versus 20 min, except for maternal flushing and warmth [23]. Part of the answer could also come from the already mentioned AMICABLE collaboration (the Antenatal Magnesium Individual Patient Data International Collaboration: assessing the benefits for babies using the best level of evidence) [16].

For as far as multiple pregnancies are concerned, in none of the studies multiple pregnancy was an exclusion criterium. Subanalysis did not demonstrate differences in the effect between singleton and multiple pregnancies in meta-analysis [20]. No data are available on repeated doses. Vaginal delivery or cesarean delivery did not seem to influence the outcome.

Is a neuroprotective effect of magnesium sulfate biologically plausible?

The neuroprotective effect of magnesium sulfate has been explained by several hypotheses. One theory states that magnesium sulfate demonstrates an anti-inflammatory effect by decreasing the production of pro-inflammatory cytokines and free radicals, leading to less apoptosis in the fetal and neonatal brain [19]. A clear relationship between pro-inflammatory cytokine levels and CP has been described [24]. In mothers that have received magnesium sulfate antepartum, neonatal monocytes from umbilical cord blood have been shown to produce less inflammatory factors including tumor necrosis factor α and interleukin-6. The production of these inflammatory factors has been shown to be directly related to the amount of magnesium in umbilical cord [24]. Furthermore, it has been demonstrated that magnesium blocks maternal cytokine production and the decrease of cytokine production is directly related to the amount of intracellular magnesium in maternal blood [25]. Another hypothesis that has been proposed is downregulation of excitatory impulses from the central nervous system, specifically downregulation of the *N*-methyl-D-aspartate (NMDA) receptors in the central nervous system, resulting in less calcium influx in brain cells leading to less electric activity and action potentials. In case of cerebral ischemia, an increase in the calcium influx in neurons has been noted especially through the voltage-dependent L-type and M-type calcium channels, regulated through the NMDA-receptor. Both the voltage-dependent calcium channels and the NMDA-glutamate receptor are blocked by magnesium [26]. Magnesium sulfate also demonstrates a direct hemodynamic effect: blocking the voltage-dependent calcium channels in the vascular wall leads to cerebral vasodilatation, resulting in an increased cerebral blood flow in the fetal and neonatal brain possibly counteracting the effects of hypoxia and ischemia on these tissues. It is these same theoretical pathophysiological mechanisms that probably explain why magnesium sulfate is the preferred prevention and treatment in eclamptic convulsions [21, 27]. Other authors have demonstrated an increased blood flow in the umbilical artery and fetal cerebral vessels [28]. Magnesium has an inhibiting effect on thrombocyte aggregation, resulting in an increased blood flow, or further enhanced by magnesium-induced increase in red blood cell deformability [29, 30]. Another contributing mechanism can be the inhibition of nitric oxide production by magnesium in neurons after oxygen–glucose deprivation [30]. In general, then magnesium seems to act on inflammatory cells, neurons, the vascular wall, red blood cells and thrombocytes.

What are the side effects and risks of magnesium in pregnancy?

Combined data from the available RCTs do not demonstrate an increase in fetal, neonatal or pediatric mortality after the administration of antenatal magnesium sulfate.

Recently attention has been drawn to possible side effects when combining magnesium sulfate and nifedipine. Both magnesium and nifedipine block calcium channels although another channel type is concerned; nifedipine mainly blocks L-type voltage-gated channels whereas magnesium has its major effects probably on the N-type channel [31]. Studies in pre-eclampsia demonstrated that the combination of nifedipine with magnesium sulfate does not lead to a rise in myocardial depression but on the contrary leads to improved cardiac function [32–34]. It has been known that in case of treatment of pre-eclampsia, magnesium toxicity resulting in maternal respiratory depression and eventually leading to maternal death is a real danger.

For the neonate, hypermagnesemia carries a theoretical risk for respiratory suppression, hypotonia, absent or diminished peripheral reflexes and in severe cases stupor or coma. These symptoms have been described in newborn babies after intra-uterine exposure to extremely high doses of magnesium sulfate to prevent eclampsia. Some concern was raised when in 2013 Kim et al. [35] published data demonstrating that in extremely preterm babies with an extreme low birth weight, mortality was related to the serum magnesium level in the neonate; at a level above 1.6 mg/dl magnesium a significant increase in neonatal mortality was noted. Furthermore, the neurological development score at 9 months both the MDI (Bailey's Mental Development Index) as the PDI (Bailey's Psychomotor Development Index) decreases inversely with an increase of serum magnesium at birth. This study included babies that had not been treated antenatally with magnesium sulfate. Probably serum magnesium is not the correct measure to use and intracellular magnesium reflects better the results of magnesium administration. Serum magnesium reflects dysfunctional magnesium capture intracellularly or even leakage from intracellular magnesium to the serum. Intracellular magnesium in peripheral red blood cells might not be representative for the effects at the level of neurons in the central nervous system.

Mittendorf et al. [5, 36, 37] demonstrated that when high doses of magnesium were used for long-term tocolysis or long-term treatment of pre-eclampsia, infant mortality increased including more intraventricular bleeding and more lenticulostriatal vasculopathy [38]. Lenticulostriatal vasculopathy is a rather specific lesion at the level of the basal ganglia associated with linear metal containing deposits. This cerebral lesion has only been described when the mother had received more than 50 g of magnesium. Probably this is a chronic loading effect that has never been described when lower total doses had been used. When using a loading dose of 4 g followed by a sustaining dose of 1 g/h, one should stop treatment after 46 or 48 h to avoid giving more than 50 g of magnesium.

Fetal hypotonia has only been described after very high doses, for example using 6 g of loading dose and then giving 2–3 g/h for many hours or even days. Fetal hypotonia is directly related to serum magnesium levels [39]. In May 2013, the American Food and Drug Administration (FDA) advised against the long-term use of magnesium sulfate as a tocolytic. This concerns using magnesium sulfate intravenously for more than 5–7 days [40]. As already mentioned magnesium sulfate is not a tocolytic. It continuous to be used as a tocolytic in the United States but has almost never been used as such in Europe.

Long-term maternal magnesium administration leads to a low serum calcium and skeletal problems, especially osteopenia and fracture both in mother and child. The FDA report is based on 18 cases of fetal/neonatal demineralization of the long bones, the mean duration of administration was 9.6 weeks intravenous magnesium, and the mean dose reaching 3.7 kg magnesium per patient.

It may be clear that neither the dose nor the administration time is what is aimed at in case of fetal neuroprotection. In September 2013 the American College of Obstetrics and Gynecology (ACOG) released a committee opinion advising to continue using magnesium sulfate in case of pre-eclampsia, eclampsia and threatening preterm birth before 32 weeks, for fetal neuroprotection and this for a maximum of 48 h [41, 42].

Concerning fetal risks at long term the individual trials have never noted any significant differences for any other relevant neonatal morbidity including bronchopulmonary dysplasia, neonatal convulsions and necrotizing enterocolitis though not all trials have reported these outcomes. Yokoyama et al. [43] found lower serum calcium and lower mean serum alkaline phosphatase in newborns who had received antenatal magnesium versus a control group. In a single case report Wedig et al. [44] described severe bone demineralization after intravenous treatment with magnesium sulfate for 8 weeks.

A vasodilatory influence, both on the umbilical artery as on the middle cerebral artery, has been described, but only after 34 weeks of gestational age. Suppression of thrombocyte aggregation has also been described in children after antenatal magnesium sulfate, as already mentioned.

What can be concluded at this moment concerning maternal magnesium sulfate?

Recently, Brok et al. [45] pointed out to a methodological problem in meta-analysis and have used the neuroprotective effect of magnesium sulfate as an example. In case the supposed random error (i.e. spurious chance findings) used in standard statistic techniques for meta-analysis is not correct and is underestimated (as simulation and empirical studies have shown), correction of the standard error makes

the results of meta-analysis non-significant (whereas by not compensating for the higher random error one falsely concludes that differences are significant). These authors have demonstrated the possibility of this methodological bias for the effect of magnesium sulfate on fetal/neonatal neuroprotection. For this reason, Huusom et al. [46] have proposed a new randomized placebo-controlled trial, the MASP (Magnesium Sulfate for Preterm Birth) to allow to enlarge the number of cases available for meta-analysis and correct for eventual random errors. They based the number needed for their trial on trial sequential analysis to avoid false-positive type 1 errors due to multiple testing. MASP trial will include 1,240 patients.

A short course of antenatal magnesium sulfate significantly diminishes the risk for CP, more obvious before 30–32 weeks of gestational age. Different international organizations have formulated advice concerning the use of intravenous magnesium sulfate for fetal neuroprotection in threatening preterm labor. The American College of Obstetrics and Gynecology has, together with the Society for Maternal Fetal Medicine, published a clinical opinion in March 2010 stating that the available studies suggest that magnesium sulfate diminishes the risk for CP in surviving infants significantly and advises to administer magnesium sulfate [41]. They do not propose a preferred dose, just suggesting that one of the dosing schedules of the studies should be used.

In Australia in 2010, a national clinical guideline was introduced advising intravenous magnesium sulfate for fetal neuroprotection at a gestational age below 30 weeks [20]. The Australian guideline advises a loading dose of 4 g over 20–30 min followed by 1 g/h for a maximum of 24 h. In case of planned delivery, treatment should be started at least 4 h before the intervention. The same treatment is appropriate for singletons and multiple pregnancies and no difference is made concerning parity, cesarean or vaginal delivery or the concomitant administration of corticosteroids. The Canadian Society of Obstetrics and Gynecology introduced, in May 2011, a Clinical Practice Guideline [47] stating that women with threatening preterm labor before 32 weeks need to receive antenatal magnesium sulfate, stopping treatment when preterm birth is no longer threatening or after a maximum of 24 h.

The Canadian guideline states that when magnesium sulfate is started, tocolysis should be stopped. The American and Australian guidelines on the contrary do not exclude the combination of tocolysis and magnesium sulfate. The Canadian guideline proposes a loading dose of 4 g over 30 min, followed by 1 g/h administration, identical to the Australian scheme. They also advise to start 4 h before birth in case of a planned preterm birth.

None of these guidelines provide guidance about repeating or not repeating magnesium sulfate, when after a period of preterm labor and successful tocolysis, preterm labor starts over again, but as demonstrated in the BEAM trial reinduction of magnesium sulfate does result in significantly less CP in the retreatment group [9].

Ow et al. [48] have studied the feasibility of implementing magnesium sulfate for neuroprotection in daily clinical practice and have shown that a high level of magnesium coverage in infants born before 32 weeks with minimal maternal toxicity and complications can be achieved.

The problems of the gestational age period in which magnesium sulfate is efficient, the optimal dosing scheme, the optimal duration of administration and the follow-up of patients will hopefully be resolved by further results from IRIS, AMICABLE and MAGENTA trial. The MASP trial will help to determine the magnitude of the effect of magnesium on neonatal brain damage.

Conclusion

At this moment use of intravenous maternal antenatal magnesium sulfate is evidence-based practice for fetal/neonatal neuroprotection in case of threatening preterm labor below 32 weeks of gestational age. The effect diminishes with the gestational age and there is not yet an evidence-based optimal dosing scheme.

Conflict of interest None.

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