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Magnesium sulphate for fetal neuroprotection

Sulfato de magnésio para neuroproteção fetal

Editorial

Introduction

Cerebral palsy (CP) is a group of disorders characterised by motor and/or postural dysfunction of a non-progressive nature commonly associated with cognitive impairment[1]. The prevalence of CP is 2/1,000 live births[1], with principal obstetric risk factors being preterm birth (particularly less than 34 weeks) and very low birth weight (less than 1,500g)[2]. Approximately 42% of all cases of CP are associated with preterm birth (Australian Cerebral Palsy Register Group)[3] with the rate of disorders amongst neonatal survivors born at less than 28 weeks gestation up to 30 times higher compared with infants born at term[1].

CP has a severe impact for the health care system. In Australia, for example, the cost of CP to the Australian community is around US$3.8 billion per annum[3]. The Centers of Disease Control and Prevention estimates the lifetime costs – including direct medical (physician visits, hospital stays, medication, assistive devices, long-term care), direct non-medical (home and automobile modifications, special education), and indirect (productivity loses) – for all people born with CP in 2000 to be $11.5 billion. The estimated lifetime cost of CP is US$1 million per case[4].

To date, there have been limited antenatal strategies to prevent this devastating outcome, but encouraging results from meta-analysis[5-7] using several large and well-designed trials[8-12] confirm that administration of magnesium sulphate ($MgSO_4$) improves the neurodevelopmental future of preterm infants.

The importance of preterm birth

The Canadian preterm birth rate overall reached 8.2% of live births in 2004, with births at <32 weeks representing 1.2% of live births in Canada[2].

The rate of preterm birth is increasing in many countries, with recently reported rates of 12.8% in the United States (National Center for Health Statistics 2009), over 8% in Australia (AIHW 2009) and over 7% in New Zealand (New Zealand Health Information Service 2006), with corresponding increases in the number of babies at risk of death or an adverse neurological outcome[3]. Information published by the Ministry of Health in Brazil showed that preterm birth rate is stable in the last few years with mean of 6.6%, with some metropolis reaching 9%[13].

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Recebido
20/06/2011

Aceito com modificações
30/07/2011

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The survival of infants born preterm has improved with interventions such as antenatal corticosteroids and surfactant. However, survival has been associated with substantial risk of medical and neurodevelopmental impairment[14].

Clinically, the most frequent adverse neurological outcomes associated with preterm birth are CP and cognitive impairment[14]. More than 50% of very preterm babies suffer from learning or motor disabilities or school difficulties, compared with about 20% of normal birthweight controls[15].

Magnesium sulphate for neuroprotection

Magnesium sulphate is widely available and commonly used worldwide in obstetric practice for eclampsia prophylaxis and treatment. Magnesium sulphate is no longer recommended for tocolysis because it is ineffective[16].

In the 1990s, observational studies suggested an association between prenatal exposure to $MgSO_4$ and less frequent subsequent neurologic morbidities[17]. Subsequently, several large randomized prospective clinical trials have been performed to evaluate the utility of $MgSO_4$ for fetal and neonatal neuroprotection. Table 1 presents a summary of these studies. The five trials examining the impact of magnesium sulphate on CP have been the subject of a Cochrane review[16] and three meta-analyses in 2009[5-7].

Although the effectiveness of $MgSO_4$ for prevention and treatment of maternal eclampsia is well proven, there remains a lack of understanding of how it may act as a neuroprotective agent. Magnesium acts in many intracellular processes, and its actions include cerebral vasodilatation, reduction in inflammatory cytokines and/or oxygen free radicals, and/or inhibition of calcium influx into cells[14]. Theoretically, $MgSO_4$ might be neuroprotective due to effects on cellular metabolism, cell death or injury or blood flow to the brain.

The Cochrane and three other systematic reviews have all come to similar conclusions and so the summary of the Cochrane review is presented:

- antenatal $MgSO_4$ had no overall significant effect on mortality (fetal, neonatal and later) (RR=1.04; 95%CI=0.92-1.17). This was an important negative finding since concerns were raised from one of the earlier trials that the reduction in CP may have been achieved at the expense of increased death rates in the $MgSO_4$ group. The finding was unaltered when confined to those where $MgSO_4$ was given specifically for neuroprotective intent;
- $MgSO_4$ significantly reduced the risk of CP (RR=0.68; 95%CI=0.54-0.87) and this remained significant when only the four trials in which magnesium with neuroprotective intent were considered (RR=0.71; 95%CI=0.55-0.91). A similar magnitude of risk reduction was seen for moderate to severe CP (RR=0.64; 95%CI=0.44-0.92) and substantial gross motor dysfunction (RR=0.61; 95%CI=0.44-0.85);
- there were no significant differences observed for the major maternal outcomes of death (RR=1.25; 95%CI=0.51-3.07), cardiac arrest (RR=0.34; 95%CI=0.04-3.26) or respiratory arrest (RR=1.02; 95%CI=0.06-16.25). Significantly more women ceased therapy in the magnesium group (RR=3.26; 95%CI=2.46-3.51). Regarding secondary maternal outcomes, magnesium therapy was associated with significantly more hypotension (RR=1.51; 95%CI=1.09-2.09) and tachycardia (RR=1.53, 95%CI=1.03-2.29). There were no differences seen in rates of maternal respiratory depression, postpartum haemorrhage or caesarean delivery;

Table 1 - Characteristics of controlled trials*

Study	Gestation	Inclusion	Exclusion	Pregnancies	Fetuses	Regimen	Follow-up
Mitendorf MagNET	25-33 weeks	Singleton or twins, preterm labour	Non-reasuring fetal status, infection or pre-eclampsia	149	165	4 g load only (neuroprotection arm)	18 months
Crowther ACTOMgSO$_4$	<30 weeks	Singleton or twins Delivery expected within 24 hours	Secong stage of labour, this pregnancy received $MgSO_4$	1062	1255	4 g load; 1 g/hour maintenance	24 months
Marret PREMAG	<33 WEEKS	Singleton, twins, triplets. Delivery expected within 24 hours	Fetal abnormality, emergency caesarean delivery, contraindication to magnesium	573	688	4 g load only	24 months
Rouse BEAM	24-31 weeks	Singleton or twins. High risk for preterm delivery, preterm PROM, preterm labour (4-8cm), indicated delivery	Delivery anticipated <2 hours, major abnormality, PROM <22 weeks	2241	2444	6 g load; 2 g/hour maintenance	24 months
Duley MAGPIE	All gestation	Pre-eclampsia and uncertainly whether $MgSO_4$ indicated	Myasthenia, hepatic coma, CI to magnesium	1544	1593	4 g load; 1 g/hour maintenance, or 5 g IM four-hourly	18 months

Magnesium sulphate was given in the first four of these trials with specific neuroprotective intent, although MagNET had both a neuroprotective and tocolytic arm.

MAGPIE was designed to prevent eclampsia, not for neuroprotection, but data was provided from MAGPIE regarding women at less than 37 weeks to contribute to the meta-analysis.

* Adapted from The Antenatal Magnesium Sulphate for Neuroprotection Guideline Development Panel[3].

- the "number needed to treat" (NNT) will rise in parallel with increasing gestational age, given the reducing incidence of CP with advancing gestation. In these trials, the absolute risk of CP was 3.7% among those treated and 5.4% in those receiving the placebo. This relative risk reduction (31%) translates an absolute risk reduction of 1.7% and therefore the number of women needed to treat to benefit one baby was 63. Among those infants delivered at less than 28 weeks gestation, where the background incidence of CP is much higher, the NNT was only 29. It should be noted that both of these NNTs compare favourably with the approximately 70 women with preeclampsia who need to be treated to prevent one eclamptic fit[18].

Magnesium sulphate produces flushing, sweating, and a sensation of warmth by its peripheral vasodilator effects when infused intravenously. Other reported maternal side effects, related to dosage and speed of infusion, include nausea, vomiting, headache, palpitations and, rarely, pulmonary oedema. Administration of $MgSO_4$ to concentrations above the recommended therapeutic range can lead to respiratory depression, respiratory arrest, cardiac arrest and death.

In the neonate, hypermagnesaemia can lead to hyporeflexia, poor sucking, and, rarely, respiratory depression needing mechanical ventilation.

In the Conde-Agudelo and Romero[5] meta-analysis, $MgSO_4$ given with neuroprotective intent was not associated with a difference in Caesarean section (822 [42.9%] in the magnesium arm *versus* 834 [42.8%] for placebo; RR=1.0; 95%CI=0.9 to 1.1; 3 trials, 3,867 women) or severe postpartum hemorrhage (28 [3.4%] in the magnesium arm *versus* 26 [3.2%] for placebo; RR=1.1; 95%CI=0.6 to 1.8; 2 trials, 1,626 women). None of the trials reported length of labour or augmentation of labour.

International guidelines

Australian National Clinical Practice Guidelines were published in March 2010 by the Antenatal Magnesium Sulphate for Neuroprotection Guideline Development Panel. They recommended antenatal $MgSO_4$ for fetal neuroprotection (excellent evidence) in the same dosage as recommended in these guidelines. However, magnesium was recommended only at <30 weeks gestation (good evidence)[3]. Also in March 2010, the American College of Obstetricians and Gynecologists issued a committee opinion on $MgSO_4$ for fetal neuroprotection. It stated that "the available evidence suggests that magnesium sulphate given before anticipated early preterm birth reduces the risk of cerebral palsy in surviving infants". No official opinion was given on a gestational age cut-off, but it was recommended that physicians develop specific guidelines around the issues of inclusion criteria, dosage, concurrent tocolysis, and monitoring in accordance with one of the larger trials[19].

In May 2011, the Society of Obstetricians and Gynaecologists of Canada issued their committee opinion recommending that antenatal $MgSO_4$ administration should be considered for fetal neuroprotection when women present at ≤31+6 weeks with imminent preterm birth, defined as a high likelihood of birth with or without preterm labour rupture of membranes, and/or planned preterm birth for fetal or maternal indications in the same dosage as recommended in these guidelines[14].

Clinical recommendations (adapted from The Antenatal Magnesium Sulphate for Neuroprotection Guideline Development Panel[3])

A summary of clinical recommendations is presented in Table 2.

Table 2 - Summary of clinical recommendations*

Clinical recommendations	Grade of recommendation
In women at risk of early preterm* imminent# birth, use magnesium sulphate for neuroprotection of the fetus, infant and child:	
*When gestational age is less than 30 weeks	A
#When early preterm birth is planned or definitely expected within 24 hours	B
(When birth is planned, commence magnesium sulphate as close to four hours before birth as possible)	A
Intravenously with a 4g loading dose (slowly over 20-30 minutes) and 1g per hour maintenance dose via IV route, with no immediate repeat doses. Continue regimen until birth or for 24 hours, whichever comes first	C
Regardless of plurality (number of babies in utero)	B
Regardless of the reason women (at less than 30 weeks gestation) are considered to be at risk of preterm birth	B
Regardless of parity (number of previous births for the woman)	B
Regardless of anticipated mode of birth	B
Whether or not corticosteroids have been given	B

*Adapted from The Antenatal Magnesium Sulphate for Neuroprotection Guideline Development Panel[3].

Dose and timing

Using a 10 mL vial of $MgSO_4$ prepare 4 g (i.e. 8 mL) of $MgSO_4$ 50% in a 10 mL syringe, configure the pump to accept the 10 mL syringe and set the pump to 32 mL an hour for 15 minutes as loading dose. For maintenance rate once the loading dose has been completed, using a 50 mL vial of $MgSO_4$ prepare 50 mL of $MgSO_4$ 50% in a 50 mL syringe, re-configure the pump to accept the 50 mL syringe and set the pump to administer the maintenance rate of 1 g/hour (2 mL/hour) or as ordered. Continue regimen until birth or for 24 hours, whichever comes first.

If birth before 30 weeks is planned or expected to occur sooner than 4 hours (e.g. scheduled caesarean or late presentation to hospital), administer $MgSO_4$ to women at risk of preterm birth, as there is still advantage likely from administration within this time. In situations where urgent delivery is necessary because of actual or imminent maternal or fetal compromise (e.g. severe fetal distress or antepartum haemorrhage), then birth should not be delayed to administer $MgSO_4$.

In the event that birth does not occur after giving $MgSO_4$ for neuroprotection of the infant, and preterm birth (less than 30 weeks gestation) appears imminent again (planned or definitely expected within 24 hours), a repeat dose of $MgSO_4$ may be considered at the discretion of the attending health professional.

Location of administration of antenatal magnesium sulphate

The location of administration of antenatal $MgSO_4$ intravenously to women should be determined by each individual maternity facility. During administration of $MgSO_4$intravenously, women should be regularly assessed as detailed in individual obstetric unit protocols. Resuscitation and ventilatory support should be immediately available, if needed, during administration of $MgSO_4$. If hypotension or respiratory depression occur prompt medical review is recommended. This may include cessation of $MgSO_4$. A minimum assessment should include checking pulse, blood pressure, respiratory rate and patellar reflexes before loading dose, 10 minutes after loading dose infusion has started and at the end of the loading dose infusion (20-30 minutes). The infusion should be stopped if respiratory rate decreases more than 4 breaths per minute below baseline, or it is less than 12 breaths per minute; or diastolic blood pressure decreases more than 15 mmHg below baseline level. While the maintenance infusion is running, observe any adverse effects. The minimum assessments should include checking pulse, blood pressure, respiratory rate, patellar reflexes and urine output 4-hourly. Stop infusion if respiratory rate is less than 12 breaths per minute; if patellar reflexes are absent, if hypotension occurs or if urine output is less than 100 mL over 4 hours.

Toxicity and potential interactions

Magnesium toxicity is unlikely with the regimen recommended in these guidelines and serum magnesium concentrations do not need to be routinely measured. In women with renal compromise, serum magnesium monitoring is recommended. Calcium gluconate (1 g –10 mL of 10% solution – slowly via intravenous route over 10 minutes) can be given if there is clinical concern over respiratory depression. There is a potential theoretical interaction between $MgSO_4$ and nifedipine of hypotension and neuromuscular blockade effects, although this is seldom reported in clinical practice. Regular monitoring of the mother is recommended as detailed in individual obstetric unit protocols. If hypotension occurs, nifedipine and $MgSO_4$ administration should cease and the woman should be promptly reviewed by a medical practitioner.

Implementation implications (adapted from The Antenatal Magnesium Sulphate for Neuroprotection Guideline Development Panel[3])

Changes in usual care

While intravenous $MgSO_4$ administration is standard care and in common use to prevent and treat eclampsia, as yet, fewer obstetric units around the world are using antenatal $MgSO_4$ for fetal, infant, and child neuroprotection.

Resource implications

Although $MgSO_4$ is an inexpensive drug, setting up, maintaining and monitoring $MgSO_4$ infusions will incur additional staff time. There will also be training needs, but these should be minimal as all units will have experience with $MgSO_4$ infusions to treat or prevent eclampsia. Less than 1.2% of all births occur at before 30 weeks gestation. Up to 10% of these babies will have been exposed in utero to $MgSO_4$ as procedure for prevention and treatment of eclampsia.

Changes in the way care is currently organised

It is acknowledged that while all tertiary obstetric units dealing with babies likely to be born at or before 30 weeks will already have established protocols and systems that will enable them to administer $MgSO_4$ intravenously to women at risk of preterm birth less than 30 weeks gestation, appropriate staffing structures may not be always in place to enable the safe administration of $MgSO_4$. The ideal setting for babies to be born before 30 weeks is a tertiary specialist unit. Given that the clinical indication for $MgSO_4$ is planned or definitely expected preterm birth before 30 weeks, then its use will generally be within tertiary obstetric units. Women threatening to give birth before 30 weeks in other settings, and fulfilling all other guideline criteria, may be eligible to receive $MgSO_4$ after consultation of their clinical carers with their local tertiary obstetric network, depending on the service capability and staffing of the non-tertiary unit.

Barriers to implementation

Barriers to implementation will include finding the extra time and staff required to administer $MgSO_4$ to more women. However, as $MgSO_4$ infusions, in the recommended regimens, are already widely practised for treatment of severe pre-eclampsia and eclampsia at these gestational ages, training needs should be minimal as all units will have experience. Monitoring women during and after they have received antenatal infusions of $MgSO_4$ is usually recommended and every obstetric unit should determine their own protocols for monitoring outcomes. As toxicity is uncommon in the recommended regimen in these guidelines, routine monitoring of serum $MgSO_4$ concentrations may not be required in all cases.

What's next?

Despite the strength of the data presented for $MgSO_4$ in fetal neuroprotection, there remain significant gaps in our knowledge and future research priorities have been identified. Some clinicians remain sceptical regarding the validity of the findings –given the heterogeneity of the trials and the lack of statistical significance for their *a priori* primary outcome (death or disability) and point to the need for further confirmatory data.

Further randomised trials are needed, comparing antenatal $MgSO_4$ with placebo when given to women at risk of preterm birth at 30 weeks gestation or more, that assess mortality, CP and combined death and CP.

Further randomised controlled trials are required specifically comparing[3]:

- different speeds of administering the loading dose of $MgSO_4$ to establish if slower loading reduces maternal adverse effects;
- optimal timing of the antenatal administration of $MgSO_4$ prior to preterm birth;
- loading dose *versus* loading dose plus maintenance;
- different loading doses (4 g versus 6 g);
- use of repeat doses of $MgSO_4$;
- treatment of the very preterm infant with $MgSO_4$ after birth.

Conclusion

Cerebral palsy is permanent, can result in severe sequelae for the infant, and can significantly affect the family and society as a whole. The NNT to prevent one case of CP appears justifiable and comparable with that for eclampsia prevention. Given the relative safety of $MgSO_4$ for the mother, the lack of evident risk regarding infant mortality, and the familiarity of most obstetricians with its use, MgSO4 should be considered for neuroprotection in the setting of preterm birth in countries such as Brazil.

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