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ANTENATAL MAGNESIUM SULPHATE FOR NEUROPROTECTION- RECOMMENDATIONS & GAPS IN KNOWLEDGE

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ABSTRACT

The main mechanism of neuroprotection action of magnesium is by acting as a cerebral vasodilator and blocking calcium mediated cell injury. Some studies suggest that magnesium sulphate decreases the production of free radicals and pro-inflammatory cytokines after ischemic insult. A study showed that neonates whose mothers received antenatal magnesium sulphate had higher cord levels of brain derived neurotrophic factor (BDNF), which has been shown to be protective against hypoxic brain injury in vivo.

KEYWORDS

Neuroprotection, Antenatal Magnesium, Neonatology

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Preterm birth, defined as delivery before 37 weeks of gestation, is the single most important cause of neonatal death in India. Incidence of preterm births is escalating. Globally, as many as 15 million babies are born prematurely, which constitutes around 11.1% of total births (1). With advances in neonatal care, the survival of preterm newborns has markedly improved. A study published in 2013 reported 52% survival among ELBW neonates in developing countries(2). But as many as one fourth survivors have been found to have neurodevelopmental disabilities during long-term follow up, cerebral palsy being one of the serious ones (3). Cerebral palsy (CP) is an umbrella term covering group of non-progressive, but often changing, motor impairment syndromes, secondary to lesions or anomalies of the brain arising in the early stages of development. It is the most common cause of severe physical disability in childhood. Although the etiology of CP is multifactorial, premature birth is a significant contributor. Prevalence of CP is highest in children born at less than 28 weeks of gestation (82/1000 live births) and declines with increasing gestational age, to 43/1000 live births between 28 and 31 weeks, 7/1000 between 32 and 36 weeks, and 1/1000 for those born later than 36 weeks of gestation (4). Recently, several studies have evaluated the role of antenatal magnesium sulphate to prevent brain injury in preterm infants. In this review, the authors have summarised the current evidence on the use of antenatal magnesium sulphate to prevent CP in preterm infants.

PRETERM BIRTH & BRAIN INJURY

Periventricular leukomalacia (PVL) is the most common form of brain injury that occurs in preterm births. These lesions predominantly affect white matter peripheral to lateral ventricles and seldom involve thalamus, corpus callosum and internal capsule (5). PVL is caused by inflammatory and/or ischemic insult leading to oligodendrocyte injury in a premature brain. The most common clinical manifestation of PVL is motor dysfunction (spastic diplegia), with 60-100% of patients with severe PVL developing CP (6).

MECHANISM OF ACTION OF MAGNESIUM SULPHATE AS A NEUROPROTECTIVE AGENT

The main mechanism of neuroprotection action of magnesium is by acting as a cerebral vasodilator and blocking calcium mediated cell injury (7). Some studies suggest that magnesium sulphate decreases the production of free radicals and pro-inflammatory cytokines after ischemic insult (7). A study showed that neonates whose mothers received antenatal magnesium sulphate had higher cord levels of brain derived neurotrophic factor (BDNF), which has been shown to be protective against hypoxic brain injury in vivo (8).

FINDINGS OF KEY STUDIES AND META-ANALYSES

Neuroprotective effects

The results of trials on neuroprotective effects of antenatal magnesium sulphate have been summarised in Table I. As evident, some trials have shown definite positive results while others could not demonstrate any significant effect. Most of the studies have used a loading dose {either 4 gram (9)(10) or 6 grams (11)} with or without continuous infusion following the loading dose. The meta-analyses of these RCTs have been summarised in Table II. These meta-analyses were somewhat different in their methodology & inclusion criteria but primarily showed that, there is a statistically significant reduction in CP with the use of antenatal magnesium sulphate.

Adverse effects for mother

Magnesium sulphate is commonly used in obstetrics for the prevention and treatment of eclampsia. As it has narrow therapeutic range, caution is necessary with its use. The common side-effects are flushing, nausea & vomiting. Serious, but rare adverse effects are respiratory depression, pulmonary edema and cardiac arrest. There is an increased risk of maternal hypotension especially when used with nifedipine as a tocolytic (12). The meta-analysis done by Conde-Agedulo et al (2009) showed that mothers who received magnesium sulphate for neuro-protection were more likely to experience minor side effects like flushing, nausea or vomiting but there was no increased risk of serious side-effects like death or severe postpartum haemorrhage (13).

Adverse effects for newborn

Blockage of calcium entry into cells may theoretically lead to hypotonia, respiratory depression and apnoea requiring respiratory support. However, analyses of data from BEAM (Beneficial Effects of Antenatal Magnesium Sulphate), the largest trial of magnesium for neuroprotection, did not find a difference in the rates of respiratory depression at birth (11). The meta-analyses have also not demonstrated an increased need for delivery room resuscitation in preterm neonates antenatally exposed to magnesium sulphate (13). Epidemiological studies have shown that prolonged exposure (beyond 5-7 days) to antenatal magnesium sulphate used for tocolysis is associated with increased risk of hypocalcemia and osteoporosis in the newborn. Therefore, FDA has recommended against the use of prolonged continuous infusion of magnesium sulphate for treating preterm labour (14). Recommendations of International organisations regarding antenatal use of Magnesium Sulphate for fetal neuroprotection, are summarised in Table III.

GAPS IN KNOWLEDGE

Most of the studies addressing this issue have been conducted in the

developed countries. Studies on efficacy of other interventions in perinatology have shown that the results in developing countries are not always same as developed countries. When antenatal steroids, a standard of care for reducing short term morbidities and mortality in preterm newborns, were tested in community settings in India, there was an unexpected increase in mortality (15). Similarly, therapeutic hypothermia, a standard of care for management of asphyxiated newborns in the west, has been shown to be ineffective in Low and middle income countries (LMIC) (16). This lack of treatment effect is either due to lack of optimal monitoring or the intrinsic differences in the population e.g. higher rates of perinatal infection, intrauterine growth retardation & maternal malnutrition in LMIC. A purist approach for any intervention, including antenatal use of magnesium sulphate, would be to wait for large high-quality randomised control studies in developing countries, showing their safety & efficacy for use. However, such trials would be difficult to conduct and would require follow-up till 18-22 months, for assessment of neuro-developmental outcome. Short of such data, an alternative option is to offer this drug only in tertiary care setting, where skill personnel and proper monitoring is available.

Table I: Results of key trials on antenatal use of magnesium sulphate for neuroprotection

Trial name & Location	Gestational age of study population & sample size	Dose	Results
ActoMgSO4 (17) Australia	<30 weeks, n=1062	4g loading followed by 1g/hour	Composite outcome (combined death or CP): 19.8% vs 24.0%; RR 0.83, 95% CI 0.66–1.03 Death: 13.8% vs 17.1%; RR 0.83, 95% CI 0.64–1.09 CP: 6.8% vs 8.2%; RR 0.83, 95% CI 0.54–1.27 Gross motor dysfunction: 17.0% vs 22.7%; RR 0.75, 95% CI 0.59–0.96
BEAM (11) US	<32 weeks, n=2241	6g loading followed by 2g/hour	Composite outcome (combined death or CP): 11.3% vs 11.7%; RR 0.97, 95% CI 0.77–1.23 CP (Moderate to severe) 1.9% vs 3.5%; RR 0.55, 95% CI 0.85–1.47 Gross motor dysfunction: Not considered.
PREMAG (9) & PREMAG follow-up France	<33 weeks, n=573	Single loading 4 g	Death and CP: OR 0.65, 95% CI 0.42–1.03 CP alone: OR 0.63, 95% CI 0.35–1.15 Gross motor dysfunction: OR 0.65, 95% CI 0.41–1.02 Death and/or gross motor dysfunction: OR 0.62, 95% CI 0.41–0.93

Table II: Results of meta-analyses on the use of antenatal magnesium sulphate for neuroprotection

Meta-analysis	Result
Costantine et al, 2009 (19)	Reduction in CP: RR 0.70, 95% CI 0.55–0.89 NNT 46 if <30 weeks of gestation; NNT 56 if <34 weeks of gestation
Doyle et al, 2003 (10)	Reduction in CP in the infant: RR 0.68, 95% CI 0.54–0.87 NNT 63; Absolute risk reduction- 1.60% Gross motor dysfunction in infancy: RR 0.61, 95% CI 0.44–0.85
CondeAgudel & Romero, 2009 (13)	Reduction in CP: RR 0.69, 95% CI 0.55–0.88 NNT 52 if <34 weeks of gestation Reduction in gross motor dysfunction: RR 0.60, 95% CI, 0.43–0.83

Table III: International guidelines on the use of antenatal magnesium sulphate for neuroprotection

Recommending body	Recommendation
RCOG ,(20) NICE (20)	Recommended for <30 weeks of gestation
ACOG (21)	Exact dose and gestation not mentioned
SOGC (22)	Recommended for <32 weeks of gestation

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