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Antenatal Magnesium Sulphate: Preventing Cerebral Palsy in Preterm Infants

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Magnesium sulphate is one of the two antenatal neuroprotective pharmacological agents used for preterm infants, the other being glucocorticoids such as dexamethasone.

The prevalence of cerebral palsy is 2 per 1000 live births with 41% of cases occurring in preterm infants. The risk of cerebral palsy increases with the degree of prematurity. A systematic review and meta-analysis showed a pooled prevalence per 1000 live births of 111.80 among children born before 28 weeks gestation and 1.35 for children born after 36 weeks.[1] Cerebral palsy varies in degree and can be debilitating if severe. In a review of 1,300 studies of children with cerebral palsy, 33% are unable to talk, 50% have learning difficulties, and 25% have epilepsy.[2] Preventing cerebral palsy is of utmost importance as there is no cure for cerebral palsy and the condition can have a significant impact on families and carers.

Cerebral palsy in preterm infants results from white matter injury. There is a loss of oligodendrocytes which produce myelin and an increase in astrocytes that cause scarring. The immature oligodendrocyte in the preterm infant is very vulnerable to hypoxic injury. Hypoxic-ischaemic damage causes an increase in glutamate release. Glutamate stimulates the N-methyl-D-aspartate (NDMA) receptor, resulting in an influx of calcium into the neurone, leading to neuronal death. It is hypothesised that magnesium sulphate exerts its neuroprotective effect by acting as an NDMA antagonist and decreasing extracellular glutamate, thus preventing excitotoxic calcium-induced injury to the neurone.[3]

The neuroprotective properties of magnesium sulphate for preterm infants were first reported by Nelson and Grether in 1995 in a case-control study.[4] The authors noted that very low birth weight infants (defined as infants with birth weights <1500 g) who survived to 3 years of age with cerebral palsy were less likely to have been exposed to magnesium sulphate in-utero when compared to controls (7.1% vs 36%).

The justification for administering magnesium sulphate as a neuroprotective strategy is based on randomised control trials. The 6 seminal studies are ACTOMgSO4[5], PREMAG[6], BEAM[7], MAGNET[8], MAGPIE[9] and a more recent study by Wolf et al[10]. A total of 8,576 infants were involved. The overall cerebral palsy prevalence was 5.2% in the magnesium sulphate group and 7.2% in the controls. This 2% superiority was consistent across all studies except for MAGNET, but this trial only reported on 46 infants.[8] In the BEAM study, the cerebral palsy rate was lower in the treatment group, 3.8% versus 6.4% (95% CI 0.41-0.86).[7] In the PREMAG study, the cerebral palsy was 7.0% in the treatment group, and 10.2% in the controls (95% CI 0.40-1.17).[6] In the ACTOMgSO4 study, the cerebral palsy rate was 6.8% in the treatment group and 8.2% in the controls (95% CI 0.54-1.27).[6] In the study by Wolf et al., the rate of moderate to severe cerebral palsy was 3.5% in the magnesium sulphate group and 5.6% in the control group (95% CI 0.28-1.27).[10]

A Cochrane Review in 2009 reported that antenatal magnesium sulphate was associated with a relative risk reduction in cerebral palsy of 32% (Relative Risk 0.68, 95% CI 0.54-0.87), and an absolute risk reduction of 1.7%.[11] In systematic reviews, the numbers needed to treat were estimated at 63 (95% CI 43-155) for infants <37 weeks gestation,[12] 52 (95% CI 31-154) for infants <34 weeks gestation,[12] 56 (95% CI 34-164) for infants <32-34 weeks gestation[13] and 46 (95% CI 26-187) for infants <30 weeks gestation.[13] While the benefit of magnesium sulphate for neuroprotection in infants less than 30 weeks gestation is broadly accepted, uncertainty remains as to whether these benefits apply at higher gestational ages.

Magnesium sulphate is administered to mothers at risk of preterm labour at less than 32 weeks gestation in some centres and at less than 30 weeks gestation in others.[14, 15] The dosage regimen consists of an intravenous bolus of 4 g, followed by an infusion of 1 g per hour for 24 hours or until the infant is born. There is rapid transfer of magnesium sulphate across the placenta to the fetus within 30 minutes of maternal administration. Therefore, it is of therapeutic value even when given a short few hours before birth. In practical terms, the mother needs to receive the magnesium sulphate between 20 minutes and 4 hours before delivery. No outcome differences have been reported with differing dosage regimens. A repeated dose is often recommended if delivery is deemed to be imminent and more than 24 hours have elapsed since discontinuing magnesium sulphate.

The duration of the antenatal magnesium sulphate infusion does not appear to influence its neuroprotective effects. However, what seems to be important is the proximity of the infusion to the delivery. A final magnesium sulphate exposure less than 12 hours before delivery significantly reduced the odds of cerebral palsy compared with exposure greater than 12 hours before delivery.[16]

Magnesium sulphate has been shown to be well-tolerated by neonates when given appropriately according to a standardised protocol. Meta-analyses of the major randomised control trials have not reported any adverse effects in this group.[12]

Women receiving magnesium sulphate in an appropriate manner have been reported to experience transient and minor side effects such as hypotension, tachycardia, nausea, dry mouth and blurred vision.[17] However, the Institute for Safe Medication Practices classifies intravenous magnesium sulphate as a high-alert medication. All obstetric staff who prescribe and administer IV magnesium sulphate to mothers should have training in the recognition of the signs of toxicity.

Since 2010, many countries have recommended the use of magnesium sulphate for neuroprotection. The administration of IV magnesium sulphate in preterm labour commenced at the National Maternity Hospital Holles Street in Dublin and other centres in Ireland in 2012. The Institute of Obstetricians and Gynaecologists of the Royal College of Physicians of Ireland (RCPI) published a clinical practice guideline in 2013.[14] It recommends its use for imminent preterm delivery before 32 weeks, but has qualified this statement by saying that, in situations where resources are limited, administration may be confined to those delivering less than 28 weeks gestation. NICE recommends administration of magnesium sulphate to preterm deliveries of less than 30 weeks gestation.[15]

The Vermont Oxford Network (VON) is a non-profit collaboration of over 1,400 neonatal centres worldwide dedicated to improving the quality and safety of medical care for newborn infants and their families. The network maintains a database of information regarding the care and outcomes of high-risk newborn infants. Currently, all 19 centres in Ireland that deliver newborn infants contribute data on infants born ≤1500 g and/or ≤29 weeks gestation to the network allowing neonatal outcomes to be benchmarked both national and internationally.

The median rate for the antenatal administration of magnesium sulphate for the entire network in 2012 was 42%. This has increased steadily from 48% in 2013 to 65% in 2020. However, this rate falls significantly below the reported median network rate of 86% for the administration of antenatal steroids (NMH Annual Neonatal Clinical Reports).

In September 2012, our institution began administering magnesium sulphate routinely to all women less than 30 weeks gestation in whom delivery was anticipated to occur within the next 12 hours. Based on the 2013 national guidelines, the indication for magnesium sulphate was extended to include infants delivering less than 32 weeks gestation.

The percentage of mothers receiving magnesium sulphate in our institution was 40% in 2012, increasing to 82% in 2020. If only women who deliver infants in our institution (i.e. inborn infants as opposed to outborn infants) and who deliver these infants between 23-31 weeks gestation are included, the rate of antenatal administration of magnesium sulphate in 2020 increases to 92% (NMH Annual Neonatal Clinical Report). The national rate for all infants delivering in the Republic of Ireland was 73% in 2019.[18] While rates of magnesium sulphate administration to eligible mothers in Ireland are slightly higher than those reported by the Vermont Oxford Network in 2019, our rates remain suboptimal.

The reported proportion of eligible mothers who receive magnesium sulphate varies from 68% to 87.5%.[19] The reasons for not receiving magnesium sulphate often include forgetting to prescribe it, difficulties in predicting preterm labour, shortage of staff, mother declined, and the lack of suitable guidelines and standard operating protocols. Key points for improving implementation include keeping the dosing protocol exactly the same, making the medication and giving sets readily available, engaging with all the caregivers, stressing the importance of the intervention, and creating a sense of expectation and a duty of care.[20]

The issues around antenatal magnesium sulphate in the prevention of cerebral palsy have changed over time. Initially, there were the clinical observations and the hypothesis that it may have a preventative role. Next, there were the randomised control trials showing a positive benefit. This was followed by the meta-analyses which confirmed that the benefits were statistically significant as well as investigating the safety profile of the drug. In more recent years, the emphasis has been on investigating the neuroprotective effect of magnesium sulphate on older gestational age groups and also on how best to roll-out and implement antenatal magnesium sulphate for preterm labour. In summary, considering the beneficial effects of antenatal magnesium sulphate, it is important to ensure that its administration becomes embedded into perinatal practice in this country.

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