Bolus or infusion plus bolus for magnesium sulphate for neuroprophylaxis?
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For 27 Feb 2019

Summary:

National recommendations are that both a bolus and an infusion are used.

PReCePT assess whether *any* magnesium has been used.

Magnesium infusions require intensive monitoring and therefore increase workload; adverse events have also bene reported.

The most recent meta-analysis concludes that a bolus +infusion regime is not superior to a bolus only regime.

And that some benefit is gained up to at least 32 weeks

It is therefore suggested a bolus only regime is used and that Mg is used up to 32+0 weeks.

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E**vidence base:**

1. NICE guidance (2015)

NICE reported, based on meta-analysis of 3 RCTs (ACTOMgSO4 - Crowther et al 2003; PREMAG - Marret et al 2007; BEAM - Rouse et al 2008) with a population of approximately 3000 babies, that:

a) Babies whose mothers were treated with magnesium sulphate in pregnancy (<34/40) were significantly less likely to be diagnosed with cerebral palsy (CP) at age 2.
b) In subgroup analysis, this finding was only true for women treated < 28/40. There was no difference in stillbirth, neonatal mortality, or paediatric mortality with magnesium sulphate, indicating that it is not associated with a higher risk of harm to the baby.
c) Women treated with magnesium sulphate were significantly more likely to experience an adverse effect (including: any adverse effect, an adverse effect leading to discontinuation of magnesium sulphate treatment, and drop in diastolic BP of > 15 mmHg). However, there were no documented cases of maternal cardiac or respiratory arrest

The NICE guidance recommends:

Magnesium sulphate for neuroprotection prior to 30 weeks , on balance of the evidence of neuroprotection and the maternal risks.

Using the same dose as for pre-eclampsia (loading dose 4 g then 1g per hour infusion) for pragmatic reasons, to reduce the likelihood of drug error being made (as there was no evidence to guide the use of one dosing regimen over another)

2. New Meta-Analysis: Crowther et al, Assessing the neuroprotective benefits for babies of antenatal magnesium sulphate: An individual participant data meta-analysis, 2017, PLoS Medicine.

The authors collected the individual patient information from 5 RCTs of magnesium sulphate in preterm birth (5,493 women and 6,131 babies) and performed a meta-analysis

Using this individual data (unlike previous meta-analyses which compared the aggregated data from each study). 4 of the RCTs looked at magnesium sulphate for neuroprotection (ACTOMgSO4 - Crowther et al 2003; PREMAG - Marret et al 2007; BEAM - Rouse et al 2008; MAGNET - Mittendorf et al 2002) The 5th RCT randomised women with pre-eclampsia to magnesium or placebo, and the subset of patients < 37/40 was used for this meta-analysis (MAGPIE - Altman et al 2002)

Key findings were:

a) Magnesium sulphate treatment was protective for cerebral palsy (NNT 42 – 46)
b) Magnesium sulphate treatment had no effect on stillbirth or perinatal mortality
c) No severe maternal adverse events were recorded
d) The following factors did not significantly influence the treatment effect:
    1) Reason for preterm birth (preeclampsia, preterm labour, chorioamnionitis, APH, PROM > 24h)

2) Gestational age: No significant difference between subgroups of <28/40, 28-31/40, or 32+/40 o However, the prevalence of CP decreases with increasing gestational age: <28/40 prevalence 8% (MgSO4 group), 11.2% (control); 28-31/40 prevalence 3.2% (MgSO4 group), 4.7% (control); 32+/40 prevalence 0.8% (MgSO4 group), 1.9% (control) Despite there being no significant difference between these subgroups, only the <28/40 group reaches statistical significance for a benefit from magnesium sulphate (the confidence intervals for the 28-31 and 32+ groups are much larger, and the 95% CI for relative risk crosses 1.
3) Total dose of magnesium sulphate
4) Whether maintenance therapy was used
5) Time from start of treatment to birth (<4h, 4-11h, 12+h)

The implications of this meta-analysis are that:

a) We should expand the age range at which magnesium sulphate is offered for neuroprotection as no significant difference in treatment effect was seen by gestational age o As there were very small patient numbers in the 32+ week group (2 cases in the treatment arm) the evidence is weaker for that group, hence the advice to give magnesium sulphate up to 32 weeks, rather than up to 34 weeks. By our estimates of NNT to prevent 1 case of CP (using the formula NNT = 1 / ARR with ARR the absolute risk reduction), then NNT at < 28/40 = 31.25, NNT at 28-31<40 = 66.67 and NNT at 32+/40 = 90.91.
b) The 4g bolus regimen is sufficient. We do not need to add the maintenance infusion.