

MAGNESIUM SULPHATE (Commentary)

Can perinatal use reduce the risk of cerebral palsy ?

Maternal use before preterm birth: Observational studies published in the mid 1990s (Nelson and Grether 1995; Hauth *et al.*, 1995; Schendel *et al.* 1996) suggested that preterm babies born to mothers who had magnesium sulphate during labour were less likely to develop cerebral palsy. There were those who hailed this as a major breakthrough, seeing it as evidence that magnesium acted to protect the neonatal brain in some little understood way. The results were indeed impressive – in Schendel's study exposure to magnesium during delivery seemed to reduce the risk of cerebral palsy almost 90% in babies of less than 1500 grams at birth. Others were more sceptical, suspecting that treatment with magnesium was merely picking out babies whose mothers had pre-eclampsia, because there was already substantial evidence that the outlook for these babies was better than it was for most babies weighing as little as this at birth (Paneth *et al.*, 1997; Grether *et al.*, 2000).

Now, twelve years later, we finally have the outcome of five randomised controlled trials that have looked into this rigorously. The first study to report was an American trial which recruited 149 women in preterm labour (Mittendorf *et al.*, 2002). Those with limited cervical dilatation were given magnesium sulphate primarily to see if this would stop labour progressing, and the rest to see if it reduced disability in survivors (i.e. if it had a 'neuroprotective' effect). It caused some concern when it was found that there had been many more deaths in the children exposed to magnesium (9/85 *v.* 1/80) – most of the deaths being late unexplained post-neonatal deaths. Later trials have now shown, fairly conclusively, that this was a chance finding.

The very well designed Australasian trial (Crowther *et al.*, 2003) involving 1,255 babies of less than 30 weeks gestation, where 99% of the survivors were followed for at least 2 years, suggested that, although short term maternal treatment did little to reduce the risk of perinatal death, and only slightly lowered the risk of some degree of cerebral palsy in surviving babies (5.7% *v.* 6.6%), it *did* significantly reduce the number of 2 year survivors with severe cerebral palsy (relative risk 0.53 [95% CI 0.30 to 0.92]). Four years later the result of the international MAGPIE trial (in which IV or IM magnesium was given to reduce the risk of maternal eclampsia and not to protect the fetus) became available. This very large trial did, however, recruit 1,593 babies who were delivered before 37 weeks gestation and, although most of the women had been recruited in resource-poor countries, the trial's many collaborators managed to follow up a sizable number of the babies and assess later developmental progress. Two of the 798 preterm babies exposed to magnesium who were successfully followed up developed cerebral palsy, as did 5 of the 795 control children (Relative Risk 0.40 [95% CI 0.08 to 2.05]) – a similar 'neuroprotective' trend to that seen in the Australasian trial, but in a group of babies where the proportion developing cerebral palsy was much smaller because only a few had been born more than 8 weeks early.

A French trial (Marret *et al.*, 2007), involving 688 babies of less than 33 weeks gestation (which used pre-discharge ultrasound evidence of cerebral injury as a surrogate way of predicting which babies would later develop cerebral palsy), found a similar trend (odds ratio 0.86 [95% CI 0.55 to 1.34]). More importantly, when all but 10 of these children were followed up two year later (Marret *et al.*, 2008), sustained benefit was clearly seen. They found a nearly significant reduction in death or cerebral palsy (odds ratio 0.65 [0.42 to 1.03]) and in death, cerebral palsy or cognitive dysfunction (odds ratio 0.68 [0.47 to 1.00]) and a significant reduction in what they termed death or 'gross motor dysfunction' (odds ratio 0.62 [0.41 to 0.93]).

The result of the recent large American trial was also published in August 2008 (Rouse *et al.*, 2008). This study involved 2,444 babies of less than 32 weeks gestation, and over 95% of the survivors were followed for the specified 2 years. This again found no difference in the risk of death or cerebral palsy (relative risk 0.97 [95% CI 0.77 to 1.23]), but it did find a significant decrease in the number of surviving babies with some cerebral palsy (4.2% *v.* 7.3%) and a particularly marked fall in the number with moderate or severe cerebral palsy (1.9% *v.* 3.5%) yielding a relative risk of 0.55 [95% CI 0.32 to 0.95). As Marret *et al.* stress in their recent overview, other important but more subtle differences in outcome may only become clear when the children are reviewed afresh when they have started school.

The conclusion seems to be that giving 40 ml of an infusion containing 0.1 g/ml magnesium sulphate over 30 minutes to mothers at imminent risk of delivering a very preterm baby within a matter of hours (with or without a sustained infusion of 1 g/hr for the next 12–24 hours) does not reduce the risk of fetal or neonatal death, but does deliver a significant reduction in the risk of moderate or severe cerebral palsy. That risk only exceeds 1% in babies of less than 33 weeks gestation (Drummond and Colver, 2002), but the risk rises to 5% in babies born at 30 weeks gestation and is about 8% in babies born at 28 weeks gestation.

Most of the women recruited into the Australasian and French trials were in premature labour, but most of the women in the American trial had suffered preterm prelabour rupture of membranes. Lex Doyle's updated Cochrane review (which now has data on over 6,000 babies) found that 5% of all the surviving

babies in the control group developed cerebral palsy but only 3.4% of those exposed to magnesium sulphate, so it is clear that the women recruited into these trials must have been at above average risk of delivering a baby with cerebral palsy. Given that the only maternal side effects were of a minor nature and treatment had no adverse effect on perinatal loss, many will now press for the wider adoption of this way of reducing the risk of cerebral palsy associated with very preterm birth. The relative risk for cerebral palsy quoted in the most recent version of Lex Doyle's Cochrane review is 0.68 (95% CI 0.54 to 0.87).

Use in the term baby after birth: A range of studies have suggested that use can reduce the cerebral damage caused by an asphyxial insult in animals (McDonald *et al.*, 1990; Spandou *et al.*, 2007). There has, however, been very little study, as yet, of the drug's post-delivery use in the human baby. One reason for this may be because it was widely believed that one still unpublished, MRC-funded, trial undertaken more than 12 years ago in the UK, which was stopped early when it became clear that there had been confusion over the dose to be used (Ramsey, 1998), failed to show any evidence of benefit. However, two small, recently published, trials from Japan and India (Ichiba *et al.*, 2002; Bhat *et al.*, 2009) have now suggested that giving term babies with clear features of severe early-onset encephalopathy **can** reduce the number who are still displaying some neurological abnormality at discharge. The babies in both these studies were given a 250 mg/kg dose of magnesium sulphate IV on three occasions 24 hours apart, and the first dose was given within six hours of birth. Unfortunately the longer term outcome for the children in these two trials has not been reported, and may never become known, although the group responsible for the Japanese trial did recently report that, when they followed thirty babies who *had* been so managed, they found the 18-month outcomes to be better than might have been expected (Ichiba *et al.*, 2006).

More studies are clearly called for to show whether use can deliver long term as well as short term benefit, and whether it can further enhance the protection that seems to be provided by elective body cooling. Any such treatment must be considered 'experimental' until these further studies have been done – there were only 17 babies in the active treatment arm of the Japanese study and 20 in the active treatment arm of the Indian study. There had initially been substantial concern that treatment with magnesium sulphate could cause hypotension but Professor Levene and his colleagues had established by 1995 that although this was indeed a problem with high dose treatment, a 250 mg/kg dose did not normally cause systemic blood pressure to fall (Levene *et al.*, 1995). However, although dopamine was used prophylactically in the Japanese trial for this reason, use was not found to be necessary in the Indian trial. Nevertheless, anyone planning to use such a strategy does need to be aware that a 250 mg/kg IV dose can occasionally cause respiratory depression. Neither is there any evidence that use is of any value in the management of traumatic head injury either in children (Natale *et al.*, 2007) or in adults (Temkin *et al.*, 2007).

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Making drugs of no commercial value more widely available

Eclampsia in the UK is now only half as common as it was fifteen years ago (2·7 cases for every 10,000 births), and serious morbidity is now only a third as common as it was back in 1992 (Knight, 2007). Clinicians are convinced that greater use of magnesium sulphate accounts for much of this change. Sadly, those working in many third world countries still experience great difficulty in getting access to simple medicines of known utility but little commercial value, and there is probably no better example of this than the continued unavailability of a safe and reliable supply of magnesium sulphate for IV use (Sevene *et al.*, 2005). The regulatory authorities have long placed an over-reliance on market forces to provide something when there is a clear need for it – forgetting that the cost of getting regulatory approval may make it unrealistic to expect any commercial company to develop such a product. It could be argued that the authorities bear a heavy moral burden for their failures to address such issues. Caffeine (q.v.) is a further product of known efficacy for which similar considerations apply.

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Use in tetanus

Magnesium sulphate has been used to induce muscle relaxation in patients with tetanus for more than a hundred years, and a trial involving 256 adults in Vietnam with tetanus severe enough to require tracheostomy to control laryngospasm has recently shown that, while an intravenous loading dose of 40 mg/kg of magnesium heptahydrate over 30 minutes followed by 1·5–2·0 g/hr, did not significantly reduce the need for mechanical ventilation (odds ratio 0·71 95% CI 0·36 to 1·40), it did reduce the need to use other drugs to control muscle spasm and cardiovascular instability. There is no published data relating to the use of such a strategy for managing neonatal tetanus.

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