

NITRIC OXIDE (Comment)

Another trial of prophylactic early use in the very preterm baby

The results of two trials of early prophylactic use appeared in 2003 and 2006. Treatment did not significantly reduce the incidence of bronchopulmonary dysplasia – the condition for which nitric oxide was ostensibly being given – but it *did* seem to reduce the number of deaths (relative risk for the two trials combined 0.77 [95% CI 0.60 – 0.98]). Mean gestation was 27.2 weeks in the babies in Schreiber's trial, and 25.6 weeks in Kinsella's trial. The failure to achieve a significant reduction in the risk of bronchopulmonary dysplasia was all the more disappointing however, because 56% of the babies in Schreiber's trial and 73% of the babies in Kinsella's trial had died or were still oxygen dependent at a postmenstrual age of 36 weeks. These were, therefore, the very babies where the need to minimise the risk of chronic lung damage is highest.

Schreiber *et al.*, 2003, randomised 207 ventilated babies of less than 34 weeks gestation to receive early inhaled nitric oxide or placebo, and also to treatment with intermittent mandatory ventilation or high-frequency oscillatory ventilation for 7 days before they were three days old. The infants in this single centre study all had a birth weight of less than 2000g (mean 989 grams) and had a median oxygen index (OI) of 7 when recruited, and those randomised to treatment with 5–10 ppm of nitric oxide were less likely to be dead or still oxygen dependent at a postmenstrual age of 36 weeks. They were also less likely to have severe intraventricular haemorrhage. However benefit was most noticeable in those babies who only had moderate respiratory distress when recruited (OI <7), and an unusually large number of the control babies had an intraventricular haemorrhage or were still oxygen dependant at 36 weeks. Those with severe disease seemed to derive little benefit. Findings at follow up were in line with the findings at discharge (Mestan *et al.*, 2005).

Kinsella *et al.*, 2006 recruited a further 793 babies of less than 34 weeks gestation who weighed 1250 grams or less at birth (mean 791 grams) from 16 study centres. All were intubated and all were still less than 48 hours old when recruited. Half of those recruited were then randomised to treatment with low dose (5 ppm) nitric oxide for an average of 12 days. Most of the babies only had moderate disease when recruited (mean OI [SD] 5.6 ± 5.9). There was no difference in the primary outcome (death or continued oxygen dependency at a postmenstrual age of 36 weeks), or in any of the individual secondary outcomes, but there was a marginal decrease (17.5 v. 23.9%) in the number of babies with some form of cerebral insult (either severe intraventricular bleeding, or haemorrhagic ventriculomegally or periventricular leukomalacia) in those given continuous low dose nitric oxide for three weeks (or until extubation). However at the Pediatric Academic Societies' Annual meeting in Baltimore in May this year it was announced that no differences were detectable in any of a range of measures of developmental disability in the two trial groups when the children were seen again two years later (Kinsella *et al.*, 2009).

Ballard *et al.*, 2006 recruited 582 babies weighing less than 1250 grams who were still ventilator dependent when 7–21 days old (mean 763 grams) from 21 centres. Babies offered nitric oxide were marginally less likely to be oxygen dependent at 36 weeks post menstrual age (56.1% v. 63.2%) but there were few other differences between the two trial groups. Those present at the meeting in Baltimore in May were told that, as might have been expected since nitric oxide was only started when the baby was at least a week old, there were no differences in the amount of neurodevelopmental impairment two years later (Keller *et al.*, 2009).

The results of a further major trial (the EUNO trial) were announced for the first time at the European Society for Paediatric Research in October 2008. It had recruited 800 babies from 35 centres across Europe. All were less than 29 weeks gestation at birth (mean weight 858 grams and mean gestation 26.5 weeks). Ninety percent of the babies had had antenatal steroids, all had already received surfactant within 12 hours of birth, and 90% were intubated at the time of recruitment. Information on the OI is only available for about half the babies, but the mean value (8.1) did not differ much from that seen in the earlier two trials, but the new trial deliberately excluded babies with severe disease (babies needing more than 50% oxygen to maintain an arterial oxygen saturation of more than 85% two hours after being given surfactant). It found **no** evidence that early low dose treatment with 5 ppm for 7 to 21 (a mean of 16) days did anything to improve survival (85.8% v. 89.5%), or the number of babies alive and no longer in oxygen at 36 weeks (65.3% v. 65.5%). Indeed, in contradiction to what Schreiber and Kinsella had found, there were slightly *more* deaths, and a hint that there had been more deaths with an intracerebral bleed in nitric oxide treated babies of less than 26 weeks gestation.

Conclusion It is now, finally, reasonably clear that offering the very preterm baby early, sustained, low-dose, prophylactic treatment with nitric oxide does almost nothing to increase survival, or to reduce the risk of the baby still being oxygen dependent at 36 weeks. Any final view as to whether early prophylaxis is 'neuroprotective', as the Schreiber and Kinsella trials had tended to suggest, will need to wait until this latest trial is reported in full, but this now looks increasingly unlikely. When the surviving babies in the Schreiber trial were seen for follow up it did look as though the cerebral ultrasound information had correctly predicted what the balance of disability would be in the two trial groups, but this has not always been the case in other trials. It

will, therefore, be very important to get follow up information in the children in the other two trials – especially as reliable information on periventricular leukomalacia was not obtained in all the children in the EUNO trial.

These recent reports mean that it has now become very difficult to advocate the **early** prophylactic use of nitric oxide, even in a further trial, at least until such time as the two year outcome of the children who were recruited into the most recent European trial becomes known – especially in the very preterm baby. As for treatment in babies with moderately serious **established** disease 7–14 days after birth (with an OI generally somewhere between 5 and 9), sustained treatment may marginally reduce the number of babies who are still oxygen dependent at 36 weeks, but it does not seem to improve survival (Ballard *et al.*, 2006) or long term outcome (Keller *et al.*, 2009) and there are other, less expensive, ways of reducing chronic oxygen dependency, as the recent caffeine trial showed (Schmidt *et al.*, 2008). Nitric oxide may occasionally be of value in a few babies of less than 34 weeks gestation if there are clear features of persistent pulmonary hypertension (Tanaka *et al.*, 2007), but there is no very little to support more widespread use.

References

- Schreiber MD, Gin-Mestan K, Marks JD, *et al.* Inhaled nitric oxide in premature babies with respiratory distress syndrome. *N Engl J Med* 2003;**349**:2099–107. [RCT]
- Mestan KK, Marks JD, Hecox K, *et al.* Neurodevelopmental outcomes of premature infants treated with inhaled nitric oxide. *N Engl J Med* 2005;**353**:23–2. [RCT]
- Kinsella JP, Cutter GR, Walsh WF, *et al.* Early inhaled nitric oxide therapy in premature newborns with respiratory failure. *N Engl J Med* 2006;**355**:354–64.
- Ballard RA, Truog WE, Cnaan A, *et al.* Inhaled nitric oxide in preterm infants undergoing mechanical ventilation. *N Engl J Med* 2006;**355**:343–53. [RCT] (See also correction 2007;**357**:1444–5.)
- Tanaka Y, Hayashi T, Kitajima H, *et al.* Inhaled nitric oxide therapy decreases the risk of cerebral palsy in preterm infants with persistent pulmonary hypertension of the newborn. *Pediatrics* 2007;**119**: 1159–64.
- Barrington KJ, Finer NN. Inhaled nitric oxide for preterm infants: a systematic review. *Pediatrics* 2007;**120**:1088–99. [SR] (See also correction 2008;**121**:451, and correspondence **121**:1287–9.)
- Dani C, Bertini G. Inhaled nitric oxide for the treatment of preterm babies with respiratory distress syndrome. [Review] *Neonatology* 2008;**94**:87–95.
- Schmidt B, Roberts R, Millar D, *et al.* Evidence-based neonatal drug therapy for prevention of bronchopulmonary dysplasia in very-low-birth-weight infants. *Neonatology* 2008;**93**:284–7.
- Keller RL, Walsh R, Vittinghoff L, *et al.* Response to inhaled nitric oxide (iNO) and neurodevelopmental impairment (NDI) in NO CLD. [Abstract] *Proceedings of the Pediatric Academic Societies Annual Meeting*, Baltimore, 2009 *E-PAS* 2009:2155:7 [RCT]
- Kinsella JP, Cutter GR, Walsh WF, *et al.* Outcomes of premature infants enrolled in the early inhaled nitric oxide for prevention of lung disease trial. [Abstract] *Proceedings of the Pediatric Academic Societies Annual Meeting*, Baltimore, 2009 *E-PAS* 2009:2155:6 [RCT]

Comment posted October 2008
and updated in June 2009