

ERYTHROPOIETIN (Commentary)

Does use in the very preterm baby increase the risk of retinopathy ?

Three Cochrane Reviews of neonatal erythropoietin use were published in July 2006. The authors managed to find 23 studies enrolling 2074 infants that looked at the effect of treatment started within eight days of birth, and showed that this had a measurable effect on the number of babies needing at least one blood transfusion, the volume of blood given, and the number of donors and transfusions to which the babies were exposed. However these reductions, though statistically significant, are of only limited clinical significance (especially as some of the children had already had at least one blood transfusion before entering the trial).

What was of real concern was that treatment was associated with a significant increase in the risk of stage ≥ 3 retinopathy of prematurity [Relative Risk 1.71 (95% CI 1.15, 2.54)], and a non-significant increase in the risk of retinopathy of *any* severity, that may possibly have been associated with the use of higher doses of supplemental iron in the actively treated children. The authors suggest there are animal data to support the view that this is not a chance finding, and observational data suggesting such a link has been accumulating for some time (Romagnoli *et al.*, 2000). Treatment did not lead to an increase or decrease in any of the other important neonatal outcome. Other observational studies attempting, retrospectively, to match babies receiving early treatment with untreated babies (Schneider *et al.*, 2008) have not always found the same increased risk of retinopathy, but matching must always be more problematic in an un-blinded, non-randomised, single centre cohort study.

The authors of these three Cochrane Reviews also found two high quality randomised double-blind trials involving 262 children that looked at the effect of treatment started *early* (< 8 days after birth) rather than *late* (8–28 day after birth). Early treatment was associated with a small non-significant reduction in the number of babies receiving one or more red blood cell transfusions [Relative Risk 0.91 (95% CI 0.78, 1.06)] but it was also associated, yet again, with a significant increase in the risk that the baby would develop some degree of retinopathy [Relative Risk 1.40 (95% CI 1.05, 1.86)] and a non-significant increase in the risk that the baby would develop severe (grade ≥ 3) retinopathy [Relative Risk 1.56 (95% CI 0.71, 3.41)].

Treatment only started when the baby is already more than a week old did not, on the other hand, have any impact on the incidence of retinopathy in the only three trials where this outcome was reported, or in the two placebo-controlled trials (involving just 212 babies) where the incidence of severe retinopathy was reported. Nor did treatment have any beneficial or detrimental effect on any other long term outcome either. The reviewers actually found 28, mainly small, randomised studies where babies receiving treatment were compared with babies receiving sham treatment, placebo treatment or no treatment, reporting a variable number of outcomes. A meta-analysis of 19 of these trials showed that treatment with erythropoietin did reduce the number of babies judged to require at least one blood transfusion after recruitment [Relative Risk 0.66 (95% CI 0.59, 0.74)]. It also reduced the total amount of blood transfused. However the difference in the amount of blood transfused was only 7 ml/kg and, since many of the babies in these studies had already had at least one transfusion before entering the trial, treatment probably only had a modest effect on the total number ever judged to need at least one transfusion after birth.

Erythropoietin is still quite widely used in some neonatal centres in America to limit exposure to blood transfusion (Von Kohorn and Ehrnekranz, 2009), but the developing consensus in Europe (Mainie, 2008) is that, aside from research into issues of its possible neuroprotective potential, there is little current justification for the use of erythropoietin in neonatal medicine except in a few limited situations – such as a concern to do everything possible to respect the views of parents who are Jehovah's witnesses (Woolley, 2005).

Could erythropoietin minimise some of the damage caused by intrapartum asphyxia

Pilot studies to look at the possible neuroprotective effect of very high dose treatment (1000–2500 units/kg) have been reported more recently (Fauchère *et al.*, 2008; Juul *et al.*, 2008; Brown *et al.*, 2009)). They were too small to show evidence of benefit, but they failed to identify any adverse effects. However there is also one small randomised study reporting apparent benefit in babies with moderate, but not severe, hypoxic ischaemic encephalopathy (Zhu *et al.*, 2009).

Potential risks of use in adult patients

While the benefits that can be derived from the use of synthetic erythropoietins has been known for some time, the potential hazards are taking longer to make themselves manifest. However a recent meta-analysis of over fifty trials (Bennett *et al.*, 2008; Bohlius *et al.*, 2009) shows that using these drugs to treat anaemia in adults with cancer can cause a small but statistically significant **decrease** in the chance of survival [relative risk 1.10, 95% CI 1.01 to 1.20]. Such treatment can also increase the risk of venous thromboembolism [relative risk 1.57, 95% CI 1.31 to 1.87]. The message has long been known, but bears repetition - almost any drug capable of doing good can also do harm. It is just that the disadvantages usually only become apparent a decade or more after the advantages.

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