A double-edged sword: Erythropoietin eyed in retinopathy of prematurity

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Erythropoietin (Epo) is an oxygen-regulated hormone produced in the kidney and released into the bloodstream. The systemic function of Epo is to stimulate erythrocyte formation in the bone marrow in response to hypoxia. Recombinant human erythropoietin (rhEpo) is used widely for the treatment of anemia in premature infants including those at high risk of developing retinopathy of prematurity (ROP). The study by Suk et al\(^1\) published in this issue of the Journal of AAPOS found that higher doses of rhEpo are associated with a higher risk of developing ROP in an age-dependent manner. This study confirms in patients the suggestion from animal studies that timing and dosing of rhEpo treatment needs to be monitored carefully with respect to ROP.

ROP is a major cause of childhood blindness and the incidence of ROP is increasing due to increased survival of premature infants with very low birth weight.\(^2\) Low gestation age/birth weight and oxygen use are major risk factors for ROP.\(^3\) After premature birth, the relatively hypoxic extra-uterine environment (compared with that in utero) suppresses production of oxygen-regulated growth factors (eg, vascular endothelial growth factor [VEGF]). This loss of growth factors inhibits the retinal vascular growth that would normally occur in the third trimester, resulting in a peripheral avascular zone. As the infant matures, the nonvascularized retina becomes increasingly metabolically active, leading to tissue ischemia and thereby increased release of hypoxia-induced growth factors, including VEGF and Epo. This growth factor excess stimulates abnormal new vessel growth at the junction between the vascularized retina and the avascular zone, which may lead to retinal detachment and blindness. Thus there is a two-phase problem in ROP. In the first phase, hypoxia suppresses oxygen-regulated factors and suppresses retinal vascular growth. This occurs up to about postmenstrual age 30 weeks. In the second phase, the avascular retina becomes hypoxic and the growth factors controlled by oxygen are highly upregulated. Normalization of each of the two phases of ROP requires an opposite approach—supplementing the suppressed growth factors in the first phase and suppressing them in the second. Furthermore, preventing vessel loss in the first phase of ROP will prevent subsequent hypoxia and will therefore prevent the second neovascular phase. Understanding the pathogenesis of ROP and in particular the role of Epo, an oxygen-regulated factor, in ROP, will help to refine the clinical care of premature infants.

Premature infants often develop anemia. This may be due in part to the oxygen-rich extra-uterine environment and suppression of systemic production of Epo in the kidney, leading to diminished erythropoiesis. Use of rhEpo to treat anemic infants began in 1990\(^4\) and has become part of neonatal care in some nurseries to decrease the need for blood transfusions. Varying doses have been evaluated in preterm infants ranging from 200 U/kg/week\(^5\) to 5000 U/kg/week.\(^6\) Although some studies have reported no differences in the incidence of neonatal morbidities including ROP\(^7,8\) between placebo and rhEpo recipients, a recent study of 390 premature infants by Brown et al\(^9\) suggests that higher cumulative use of rhEpo in preterm infants was associated with an increased risk of retinopathy progression.

The study by Suk et al\(^1\) went one step further, looking at both dosing and timing of rhEpo treatment to evaluate the effect on retinopathy. The authors compared two groups of infants admitted to Loma Linda University Children’s Hospital (119 infants admitted in 1994 when rhEpo treatment was rare, and 145 infants in 2002 when rhEpo treatment had become a standard practice there) to determine whether the use of rhEpo is an independent risk factor in the development of retinopathy. Using multiple regression analysis, the study found that infants receiving more doses of rhEpo (>20 doses) have a higher risk of developing ROP and therefore are more likely to require laser photocoagulation. In addition, infants with later rhEpo treatment (treatment initiated >20 days ago) also have a higher risk of ROP (>fourfold compared with those who started rhEpo treatment <20 days of age), suggesting that timing of Epo treatment is likely a risk factor as significant as dosing for ROP.

Why would Epo, an anemia treatment, be associated with an increased risk of developing retinopathy? Recent studies have suggested that Epo is a multifunctional, pro-angiogenic, and pro-survival growth factor that does much more than stimulate erythropoiesis.\(^10-12\) Oxygen regulates Epo production not only in the kidney but also in the
retinal vessel proliferation in a mouse model of ROP. Just as hyperoxia-induced suppression of VEGF contributes to vessel loss in ROP, lack of Epo secondary to hyperoxia contributes to retinal vascular instability in mice. Early supplementation of Epo prevents retinal vessel loss and thereby prevents secondary pathological neovascularization in this animal model.

Why do premature infants receiving higher doses of rhEpo have an increased risk of developing ROP? Infants requiring more Epo might have more severe systemic Epo deficiency because of more severe hyperoxia. Hyperoxia suppresses production of oxygen-regulated growth factors, resulting in more retinal vessel loss in the first phase, which contributes to the progression of ROP. Conversely, in the second proliferative phase, just as higher levels of VEGF contribute to pathological neovascularization, elevated levels of Epo, which are found in the vitreous of patients with proliferative diabetic retinopathy, contribute to neovascularization as well. Suppression of Epo in the second neovascular phase of retinopathy suppresses retinal vessel proliferation in a mouse model of ROP.

Late supplementation of Epo at the proliferative stage when the retinal expression of Epo is already elevated might therefore further provoke an angiogenic response and worsen retinal neovascularization. The study by Suk et al clearly suggests that rhEpo treatment at the late stage of retinopathy has an adverse effect on ROP. Early rhEpo treatment has been suggested to be more effective for treating anemia in premature infants. Whether early rhEpo treatment is also beneficial for ROP awaits further studies on restoration of Epo to normal levels in premature infants. More detailed prospective studies are required. Confirmation of the observations in Suk et al is needed. Furthermore, their study has limitations: the authors do not account for changes that occurred in clinical care during the two study periods (1994 vs 2002), and they do not account for potential bias introduced in the intent-to-treat analysis. A study analyzing the timing of rhEpo treatment with respect to postmenstrual age rather than chronological age would also be beneficial.

Together, these studies suggest that Epo might act as a double-edged sword. The timing of rhEpo treatment during different stages of retinopathy is likely critical for determining its beneficial or destructive role in ROP. rhEpo may help treat anemia, but given at the wrong time, it may worsen eye disease. These findings suggest that clinicians should know the state of the eye before considering rhEpo treatment for anemia and pause before treating a premature infant with full-blown retinopathy. However, early treatment with rhEPO may be beneficial for both alleviating anemia and preventing ROP.

References