Published in final edited form as:

J Pediatr. 2015 July ; 167(1): 10–12. doi:10.1016/j.jpeds.2015.03.054.

Erythropoiesis Stimulating Agents Demonstrate Safety and Show Promise as Neuroprotective Agents in Neonates

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Studies published 27 years ago showed that erythroid progenitor cells of preterm neonates were responsive to recombinant erythropoietin (Epo).¹ Many clinical trials were subsequently performed worldwide, testing whether administering Epo to preterm infants might be a safe and effective way to expand their red cell mass and decrease their transfusion requirements. Indeed, essentially all trials convincingly showed that Epo can stimulate erythropoiesis in preterm and term infants, and has the capability to diminish donor exposure and decrease transfusions. Recent randomized, multi-centered, placebo-controlled trials of erythropoiesis stimulating agents (ESAs), such as Epo or longer acting darbepoetin, administered to preterm infants also show a reduction in blood donor exposure and a lower transfusion rate.² Along with the clinical trials aimed at decreasing or eliminating transfusions, animal studies have shown that ESAs have neuroprotective effects, thought to be in part the result of ESA's inhibition of apoptosis. These encouraging findings paved the way for clinical trials that are currently underway, evaluating clinically relevant neurodevelopment effects of ESAs in high-risk neonatal populations. Higher doses of ESAs than those used in stimulating erythropoiesis have been proposed to achieve Epo concentrations capable of crossing the blood brain barrier to produce therapeutic levels in the brain. Doses from 1000 to 3000 units/kg have been evaluated in pilot studies of preterm infants^{3,4} and in term neonates receiving therapeutic hypothermia for hypoxic ischemic encephalopathy.⁵ Darbepoetin has been evaluated in term neonates with hypoxic ischemic encephalopathy being cooled,⁶ and in preterm infants to improve neurocognitive outcomes,⁷ with encouraging neurodevelopmental results. Although the most effective neuroprotective dose and dosing intervals of these ESAs have yet to be determined, evidence is

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The other authors declare no conflicts of interest.

accumulating that ESAs have favorable neuroprotective effects in both preterm^{7,8} and term infants.⁹

In this issue of *The Journal*, Fauchere et al report hospital outcomes of a randomized clinical trial testing high dose Epo in preterm infants.¹⁰ Although results of the primary outcome of the study—neurodevelopment at 24 months—are pending, a subset of infants enrolled in the study had magnetic resonance imaging at term-corrected age, which showed that the infants treated with Epo had lower white and grey matter injury scores.¹¹

In the current study, over 450 infants were randomized in masked fashion to receive placebo (NaCl 0.9%) or intravenous Epo, 3000 units/kg administered at 3, 12–18, and 36–42 hours after birth. This initial report focused on the safety of early high dose Epo, and followed the hospital course of all enrollees. No safety issues were identified. Specifically, there were no differences in the occurrence of any intracranial hemorrhage (11.4% in the Epo-treated group vs 9.6% in the placebo group) or of retinopathy of prematurity (ROP). The overall incidence of any stage ROP in the Epo treated group was 9.5% (1.9% for ROP stage 3), vs 10.2% (3.7% for ROP stage 3) in the placebo group.

The safety data are reassuring both to Epo investigators evaluating potential neuroprotective effects, and to clinicians currently using Epo to avoid transfusions in preterm infants.¹⁰ Although early studies of Epo administered to preterm infants were promising, meta-analyses published in 2006^{12,13} reversed the trend of Epo use in many neonatal intensive care units. The authors of the 2006 reviews separated Epo studies into early (first week of life) and late (after the first week) administration, and concluded that the incidence of stage 3 ROP was increased with early Epo administration. Only 1 study in this meta-analysis reported an increase in ROP among recipients of Epo, a single-center study by Romagnoli et al.¹⁴ In revised meta-analyses^{15,16} of the 27 studies randomizing 2209 infants to early Epo or placebo, the incidence of ROP was reported in 7 studies, comprising only 36% of all study infants. Despite their initial report in 2000, Romagnoli et al continued to study Epo,¹⁷ and Epo is currently standard of care in their unit.¹⁷

Currently, ample evidence exists that administering ESAs to selected neonatal populations significantly diminishes transfusion requirements and blood donor exposures, reduces transfusion costs, and conserves blood bank resources.^{18,19} In addition, there is mounting evidence—bolstered by recent studies including this study by Fauchere et al—indicating that early Epo administration to preterm neonates does not increase their risk for developing ROP or any other complications of prematurity. We eagerly await the long-term follow-up results of this and other studies such as the Preterm Erythropoietin for Neuroprotection (PENUT) study to determine whether high dose ESAs are also neuroprotective.

Acknowledgments

Supported by the National Institutes of Health (NIH; R01 HD059856, U01 NS077953 [to R.O.], U01 NS077953, R01HD073128, U01NS077953 [to S.J.], P01 HL046925, U01 NS077953 [to J.W.]), and Intermountain Healthcare Medical Foundation (to R.C.). J.W. is a paid consultant to HemoGenix.

Glossary

Epo	Erythropoietin
ESA	Erythropoiesis stimulating agent
ROP	Retinopathy of prematurity

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