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Impact of Erythropoiesis-Stimulating Agents on Behavioral Measures in Children Born Preterm

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Abstract

Objective—To evaluate the impact of erythropoiesis-stimulating agents (ESAs) administered during initial hospitalization and family demographic factors on behavior at 3.5–4 years of age.

Study design—Children were enrolled who had previously participated in a randomized study of ESAs (n = 35) or placebo (n = 14) in infants born preterm with birth weights of 500–1250 g. A term healthy control group (n = 22) also was recruited. Behavior was evaluated by parent report with the Behavioral Assessment System of Children-2. Principal component analyses identified 2 demographic factors, a Socioeconomic Composite (SEC) and a Family Stress Composite. A multivariate general linear model evaluated the impact of study group and sex on the 4 composite scales of the Behavioral Assessment System of Children-2. Demographic factors were treated as covariates and interactions with study group (ESA, placebo, and term) were examined.

Results—The ESA group had significantly better scores than the placebo group on behavioral symptoms ($P = .04$) and externalizing scales ($P = .04$). An interaction was observed between study group and SEC ($P = .001$). A beneficial effect of ESAs was maximal in the children with lower SEC scores.

Conclusions—The beneficial effects of ESAs on childhood behavior were maximal in children with lower SEC scores. ESAs seemed to ameliorate the adverse impact of lower SEC on behavioral domains seen in the placebo group. This effect was independent of the beneficial effect of ESAs on global cognition we reported previously.

Trial registration—[ClinicalTrials.gov](https://clinicaltrials.gov): NCT01207778 and NCT00334737.

Infants born preterm are at risk for a variety of adverse outcomes, including motor, cognitive, and behavioral problems.¹ In a national cohort study from Finland, parents of 5-

year-old children born with very low birth weight reported greater rates of behavioral difficulties including internalizing behavior (ie, anxiety, depression, withdrawal) and externalizing behavior (ie, conduct problems, aggression, hyperactivity) compared with children born term.² Behavioral problems in children with very low birth weight have been shown to persist through early childhood and adolescence and are not lessened by higher intelligence scores.³ Several studies have shown that behavior problems in early childhood often are accompanied by cognitive, executive function, and motor difficulties, raising concerns about long-term outcomes.^{4,5}

Erythropoiesis-stimulating agents (ESAs) such as erythropoietin (Epo) or darbepoetin (Darbe) have been used to increase red cell production and decrease transfusions in infants born preterm. Recent studies in animals and humans in which investigators evaluated the nonhematopoietic effects of ESAs suggest a neuroprotective potential through mechanisms of increased oligodendrogenesis, decreased inflammation, decreased oxidative injury, and decreased apoptosis.⁶ Our group reported previously that the administration of ESAs (Epo or Darbe) shortly after birth significantly improved cognition and object permanence scores and decreased neurodevelopmental impairments at 2 years of age⁷ in a randomized trial of children with birth weights of 500–1250 g.⁸ These findings persisted at 3.5–4 years of age.⁹

The purpose of this study was to describe the effects of ESAs on behavioral and emotional functioning at 3.5–4 years of age. Because socioeconomic status has diverse and prominent effects on brain development,¹⁰ the role of socioeconomic and family factors were investigated as possible modifiers of ESA effects.

Methods

Former infants born preterm (500–1250 g birth weight), enrolled at 48 hours of age in the original study⁷ were eligible for the current BRITE study (Brain Imaging and Developmental Follow-up of Infants Treated with Erythropoietin; Clinicaltrials.gov: NCT01207778). Infants with genetic disorders, significant congenital anomalies (including known neurologic anomalies), hypertension, seizures, thrombosis, hemolytic disease, or who were already receiving Epo were ineligible for the original study. The number of children eligible for the study and evaluated at 3.5–4 years of age is shown in Figure 1 (available at www.jpeds.com).

A total of 49 former children born preterm from the original randomized controlled trial were recruited successfully. A group of children born at full term (n = 24) who had an uneventful newborn course also were recruited at age 3.5–4 years at the New Mexico site for the BRITE study. Questionnaires were missing from 2 of the term group and 4 of the preterm group; those subjects were omitted from this analysis. The parents and examiners continued to be masked to the treatment assignment of the children. The study was approved by the institutional review boards at the University of Utah and the University of New Mexico, and informed consent was obtained from parents. Demographic and medical history data were obtained from the family.

Initial Study Procedures

Randomization of the participants born preterm to ESA vs placebo groups originally was performed during their initial hospitalization with the use of a computer-generated permuted block method, stratified by center. Twins were assigned to the same treatment group. Caregivers and investigators (except the research pharmacists and coordinators administering the study medicine) were masked to the treatment assignment. An investigational new drug application was approved by the Federal Drug Administration (IND #100138), and the study was registered at [ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study?term=NCT00334737) (NCT00334737).

Dosing of Study Drug and Supplements

Infants were randomized to 1 of 3 groups: Epo, 400 units/kg, given subcutaneously 3 times a week; Darbe, 10 μ g/kg, given subcutaneously once a week, with sham dosing 2 other times per week; or placebo, consisting of 3 sham doses per week. Dosing continued until 35 weeks of postmenstrual age, discharge, transfer to another hospital, or death. All infants received supplemental parenteral and enteral iron, folate, and vitamin E. All infants received study drug dosing through 35 weeks of postmenstrual age, for an average dosing length of 7.2 ± 1.8 weeks. After planned analyses showed no significant differences between Epo and Darbe recipients, they were combined as a single ESA group.

Present Study

The Behavioral Assessment of Children Scale–Second Edition (BASC-2) is a norm-referenced parent rating scale that assesses childhood behavioral and emotional issues.¹¹ The BASC-2 consists of 4 composite scales: adaptive skills (social skills, activities of daily living), behavioral symptoms (withdrawal or atypical behaviors), externalizing problems (hyperactivity, aggression, conduct problems), and internalizing problems (anxiety, depression, somatization). For the adaptive skills composite, greater scores are better; for other scales, greater scores are indicative of problems. Standardized t scores were used for analyses.

The Wechsler Preschool and Primary Scale of Intelligence – Third Edition, a widely used standardized scale of general cognitive abilities, was administered to each child.¹² Socioeconomic and demographic variables were obtained through maternal interviews, including maternal age and education, income level, the number of times the family moved since the index child's birth, the number of children in the household <6 years of age, and the primary language spoken in the home.

Data Analyses

The hypothesis of beneficial ESA treatment effects across all BASC-2 scales was tested with a multivariate general linear model with covariates (MANCOVA). With respect to the 4 dependent variables (BASC-2 scores) in the MANCOVA, preliminary analyses revealed that 3 of the 4 variables were not distributed normally, according to the Shapiro-Wilks test (all except the adaptive skills scale). A log transformation was performed for each BASC-2 scale; all transformed values correlated with the original t scores at $r = 0.99$.

Effect sizes from the MANCOVA are presented as partial eta-squared values with statistical significance of $P < .05$ for the Wilks' lambda multivariate tests. Fixed factors were study group and sex. Given the importance of demographic factors for BASC-2 scales,¹³ these influences were considered systematically in the statistical model. Rather than including each of the 7 specific demographic variables in the model, which would reduce statistical power and complicate interpretation, these variables were reduced to 2 composites via the use of principal components analysis with direct oblimin rotation. Ethnicity was coded as either "Hispanic" or "non-Hispanic." Two factors emerged with eigenvalues >1 , and these captured 37% and 23% of the shared variance (Table I, available at www.jpeds.com, provides details on factor loadings). For summary purposes, the first of these factors was termed "Socioeconomic Composite" (SEC) and the second "Family Stress Composite." Greater scores on the SEC indicated relatively greater income and education, and greater scores on the Family Stress Composite indicated more family moves, more children in the home, and younger maternal age. Preliminary analyses revealed that the second demographic factor was not related to any BASC-2 scale and did not interact with other factors, so this variable was dropped from further analysis.

In the MANCOVA, sex and study group (placebo, ESA, term) were fixed factors and SEC was a covariate. Interactions of sex with study group and SEC with study group were included because of concern that effects of ESA might be moderated by these factors. Planned comparisons contrasted the placebo and ESA groups (to reveal the effects of ESAs) and the ESA and term groups (to reveal whether ESA treatment improved scores on the set of dependent variables). For descriptive purposes independent-samples t tests and Pearson correlations and partial correlations also were conducted (significance level was $P < .05$).

Results

Infants were originally enrolled between July 2006 and May 2010. Demographic characteristics and statistical comparisons across study groups are shown in Table II. Maternal education level was not significantly different between the groups. For the full sample, 34% of the mothers had a high school education or less, and 39% had some college or a college degree. The characteristics of the children who returned for follow-up were similar to those who did not.⁹ Tests of homogeneity (Levene test of equality of variances and Box test of equality of covariance matrices) indicated that statistical assumptions of MANCOVA were met.

The 3 study groups (ESA, placebo, and term controls) significantly differed on the 4 BASC-2 scales ($P = .001$; $F[8, 112] = 3.546$, partial eta-squared = 0.202). At the univariate level, the effect of study group was significant for all 4 BASC-2 scales (all P values $< .001$). SEC also had a significant effect ($P = .002$; $F[4, 56] = 4.731$, partial eta-squared = 0.253), and its interaction with study group also was significant ($P = .015$; $F[8, 112] = 2.514$, partial eta-squared = 0.152). There was no effect for sex ($P = .580$; $F[4, 56] = 0.724$, $P = .580$, partial eta-squared = 0.049) or interaction of sex with study group ($P = .086$; $F[8, 112] = 1.790$, partial eta-squared = 0.113).

An additional multivariate generalized linear model was performed to compare the ESA and placebo groups. The effect of group fell just short of significance ($F[4, 38] = 2.48, P = .06$, partial eta-squared = 0.21). The effect of SEC was significant ($F[4, 38] = 5.67, P = .001$, partial eta-squared = 0.37), as was the interaction of SEC with group ($F[4, 38] = 5.92, P = .001$, partial eta-squared = 0.38). Figure 2 shows the interaction of study group (ESA vs placebo) and the SEC factor on BASC-2 scales when SEC was split at the median to create high and low groups.

The ESA group had significantly better scores than the placebo group on behavioral symptoms ($P = .024$) and externalizing problems ($P = .018$), but the study groups did not differ on adaptive skills ($P = .221$) or internalizing problems ($P = .517$). The term group had better scores than the placebo and ESA groups on each of the BASC-2 scales (P values ranged from .009 to .002; Table III). There were differences in neurodevelopmental impairments between groups: 4 of 14 children (29%) in the placebo group had a Full-Scale IQ of <70 , compared with 3 of 39 children (8%) in the ESA group ($P = .07$), and 3 children (21%) in the placebo group had mild cerebral palsy, compared with no children (0%) in the ESA group ($P = .016$).⁹

To evaluate the independence of these results on the BASC-2 from the ESA effects as we previously demonstrated for cognitive skills,⁹ we conducted an additional multivariate general linear model analysis. Full-Scale IQ was added as a covariate, and significance levels were virtually unchanged in both analyses. Thus, the effects of ESAs on the BASC-2 were independent of the effects of ESAs on cognition.

We further analyzed the significant interaction of study group with SEC by examining correlations of SEC with the 4 BASC-2 scales, after co-varying for sex (Table IV). In the placebo group, these were all significant and negative (ranging from $r = -0.807$ for behavior problems to $r = -0.671$ for the reverse scored adaptive behavior scale; P values all $< .02$). In contrast, in the ESA group and the term group, none of these partial correlations with SEC approached significance. Thus, the placebo group seemed especially sensitive to the adverse effects of lower SEC for BASC-2 scales.

Discussion

In this study, we examined the effects of postnatal ESA administration on a parent rating scale tapping behavioral and emotional outcomes. Because it has been demonstrated that social and demographic variables affect behavioral functioning, we explored the impact of 2 important broad dimensions of social background, which included socioeconomic and stress variables. We also examined the possibility of interactions of ESAs and these 2 social factors. The overall effect of ESAs on the 4 BASC-2 composite scores, when we took into account the social factors and their interaction with ESA administration, fell just short of significance ($P = .06$), although the effect size fell in the medium-large range. The most significant effect was the interaction of ESA group with the SEC factor (Figure 2). This effect revealed that the beneficial aspects of ESAs were maximal in the low SEC group. ESAs apparently served to mitigate the adverse effects of low SEC in the ESA-treated children. Although we have described an effect of ESA on cognition in this same sample,⁹

we found these cognitive effects were independent of the behavioral effects demonstrated here. Finally, despite these positive effects of ESAs, the ESA-treated children born preterm did not completely catch up to children born term on any BASC-2 scale.

In general, children born preterm had more behavioral symptoms, externalizing problems, and internalizing problems than did children born at term gestational age, similar to findings by Baron et al.¹⁴ They observed that children born preterm had more problems than children born term on all 4 BASC-2 scales. Spittle et al¹⁵ also found that toddlers born preterm (2 years' adjusted age) were rated by their parents on the Infant Toddler Social Emotional Assessment scale as having more internalizing and dysregulation problems. Another study that used the Strength and Difficulties Questionnaire noted that 5-year-old children born with very low birth weight had more internalizing, externalizing, and obsessive-compulsive behavior problems than a term control group.² The finding that the children born preterm treated with ESAs had less behavioral symptoms and externalizing problems on the BASC-2 than the children born preterm in the placebo group is unique to this study.

There is an expanding literature demonstrating that socioeconomic disadvantage can affect neurodevelopment adversely. In our sample, 34% of the mothers had a high school education or less, compared with 42% of the US population. We did find that 39% of the mothers had some college or a college degree, which is similar to the US population (38%).¹⁶ A recent study demonstrated that children born to socioeconomically disadvantaged parents were more likely to exhibit neurologic abnormalities during the first 7 years of life.¹⁷ A review article by Linsell et al¹⁸ found that less parental education was related to lower cognitive development in children <5 years; this effect continued during school years. Compared with term-born children, 5-year-old children born preterm had significantly lower IQ scores (up to a 14-point difference) when their parents had less education. Moreover, higher parental education level was related to fewer parent-reported behavior problems in their children.¹⁹ In the current study, we also found a significant SEC-by-study group interaction. Specifically, children with lower SEC benefited more from ESAs.

Consistent with this observation, significant correlations of SEC with BASC-2 composites were limited to the placebo group (Table IV). In a recent study, Noble et al²⁰ found that children from homes with lower family income and maternal education had differences in surface area in brain regions supporting language, executive function, and memory skills. A study in Switzerland by Leuchter et al²¹ found that compared with infants born preterm treated with placebo, fewer infants born preterm treated with Epo during the neonatal period had abnormal term-equivalent age scores on magnetic resonance imaging for white matter injury, white matter signal intensity, periventricular white matter loss, and gray matter injury. O'Gorman et al²² also reported improved white matter development as assessed by diffusion tensor imaging and tract-based spatial statistics in 24 of the infants treated with Epo compared with 34 infants treated with placebo. Our findings thus add to the evidence that ESAs may have beneficial effects in infants born preterm and, furthermore, suggest they have an enhanced beneficial effect related to behavior in infants from socially disadvantaged families.

Limitations of this study include the small number of children in each of our groups, which limits the generalizability of the findings. Also, there were differences in neurodevelopmental impairments between groups that may have impacted behavior: more children in the placebo group than the ESA group had a Full-Scale IQ < 70 ($P = .07$) or mild cerebral palsy ($P = .016$). Although our study had statistically significant results, confirmation in a larger study is needed. Although behavioral ratings are used widely, they have limitations and direct observation of the child's behaviors would be beneficial. We also did not have any measures of mother-child interactions, which have been found to impact a child's behavior and developmental outcome.^{23,24}

Our findings may have implications for the medical treatment of children born preterm when considering the possible benefits of ESAs as one component in their comprehensive medical care during the neonatal period. Larger multicenter trials evaluating neuroprotective effects of high-dose Epo are under way (Preterm Epo Neuroprotection Trial, NCT01534481) and will provide additional evidence of the effect of ESAs on the neurodevelopment of infants born preterm. Our study suggests that it is important for early intervention programs to provide services to children from more disadvantaged environments that target strategies to improve externalizing behaviors such as hyperactivity and aggression, as well as behavioral problems such as withdrawal and mood abnormality. We found that children born preterm who were treated with ESAs in the neonatal period had cognitive improvement regardless of socioeconomic factors,⁹ as well as behavioral improvements for those children from more impoverished backgrounds. It is possible that early treatment of infants born preterm with ESAs may mitigate the adverse effects of factors such as low maternal education and low income on behavior in early childhood. Although further investigation is needed, especially longitudinal studies through early school age,²⁵ these findings have important implications for improving outcomes of children born preterm.

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Glossary

Darbe	Darbepoetin alfa
Epo	Erythropoietin
ESA	Erythropoiesis-stimulating agents
BASC-2	Behavioral Assessment System of Children – Second Edition
SEC	Socioeconomic Composite

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Figure 1.

Numbers of infants that were screened for eligibility for the BRITE study, that were eligible for the study, and that were evaluated at 3.5–4 years with completed BASC-2 questionnaires. *RCT*, randomized controlled trial.

Figure 2.

The interaction of study group (ESA vs placebo) and the SEC factor on BASC-2 scales. SEC was split at the median to create high and low groups. *Bars* represent SDs. Data from children in the placebo group are represented by *white columns* and from children in the ESA group by *gray columns*. *Hatched columns* represent high SEC data. * $P < .05$, low SEC placebo group vs the other 3 columns (high SEC placebo group, low SEC ESA group, and high SEC ESA group).

Table I.

Loadings for the 2 sociodemographic factors used for principal component analysis

Factors	Socioeconomic Composite	Family Stress Composite
Income	0.70	−0.38
Maternal education	0.76	−0.37
Maternal age	0.21	−0.82
Number of family moves	−0.15	0.69
Number of children <6 y	−0.17	0.74
Ethnic background	0.72	−0.20
Primary language	−0.76	−0.30

Table II.

Demographic data

Factors	Placebo n = 14	ESA n = 35	Term n = 22	Placebo vs ESA	ESA vs term
Gestational age, wk	27.64 (1.52)	27.37 (1.74)	39.05 (1.35)	.40	<.001
Test age, mo	48.79 (3.26)	48.64 (3.69)	45.04 (2.10)	.72	<.001
Income [*]	4.00 (1.92)	4.59 (2.10)	5.09 (1.68)	.24	.74
Maternal education [†]	4.50 (1.09)	4.85 (1.20)	5.43 (1.38)	.24	.34
Maternal age, y	24.57 (4.11)	27.92 (6.87)	29.91 (7.62)	.02	.74
Number of family moves	2.29 (1.94)	1.31 (1.28)	1.22 (1.41)	.01	.69
Number of children < 6 y of age in home	2.07 (1.39)	1.59 (0.75)	1.65 (0.78)	.11	.19
Primary language				.10	.72
English	100%	83%	86%		
Spanish	0%	17%	14%		
Ethnicity				.92	.05
Hispanic	36%	37%	64%		
Non-Hispanic	64%	63%	36%		

Values shown are mean (SD) or percentiles.

^{*} Income: <\$10 000; \$10 000–20 000; \$20 000–30 000; \$30 000–40 000; \$40 000–50 000; \$50 000–60 000; \$60 000–70 000; \$70 000.

[†] Maternal education: 0, less than high school; 1, completed high school; 2, completed 1 y of college, no degree; 3, associate's degree (2 y of college); 4, completed college; 5, some graduate school, no degree; 6, completed master's degree or greater.

Table III.

BASC-2 composite scores across study groups

BASC-2 scales	Placebo n = 14	ESA n = 35	Term n = 22	<i>P</i>₁	<i>P</i>₂
Adaptive skills	50.86 (10.32)	53.40 (8.65)	60.45 (7.85)	.221	.003
Behavior symptoms	59.29 (16.23)	50.63 (11.77)	41.68 (7.23)	.024	.002
Externalizing problems	57.43 (13.32)	49.43 (11.41)	42.86 (6.83)	.018	.009
Internalizing problems	56.93 (10.51)	54.37 (11.48)	45.73 (8.60)	.517	.004

Values shown are standard score mean (SD). Significance levels were determined by independent samples *t* tests; *P*₁: placebo vs ESA; *P*₂: ESA vs term.

Table IV.

Correlations between the SEC factor and BASC-2 composite scores

BASC-2 scales	Placebo n = 14	P value	ESA n = 35	P value
Adaptive skills	0.67	.033	−0.01	NS
Behavior symptoms	−0.81	.003	−0.08	NS
Externalizing problems	−0.65	.01	−0.16	NS
Internalizing problems	−0.73	.003	−0.15	NS

NS, not significant.Values shown are correlations with corresponding *P* value.