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Effect of Blood Transfusions on Cognitive Development in Very Low Birth Weight Infants

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Abstract

Objective: Preterm infants frequently receive red cell transfusions; however, the effect of transfusions on cognition is unclear. We evaluated the relationship between transfusions and cognitive outcomes in preterm infants enrolled in a randomized trial of erythropoiesis stimulating agents (ESAs).

Study Design: Preterm infants were randomized to ESAs or placebo during initial hospitalization, and transfusions recorded. Children were evaluated using standard developmental tests of cognition at 18–22 months (56 ESA, 24 placebo) and 3.5–4 years (39 ESA, 14 placebo)

Results: Cognitive scores at 18–22 months were inversely correlated with transfusion volume at ($p=0.02$). Among those receiving ≥1 transfusion, cognitive scores were significantly higher in the ESA-treated group ($p=0.003$). At 3.5–4 years, transfusions weren't correlated with cognitive scores.

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Conclusions: In the placebo group, transfused children had lower cognitive scores than did non-transfused children at 18–22 months. In the ESA group, cognitive scores did not differ by transfusion status, suggesting ESAs provide neuroprotection.

Keywords

prematurity; erythropoietin; darbepoetin; neuroprotection

Introduction

Preterm infants who receive red blood cell (RBC) transfusions are more likely than matched un-transfused controls to experience common morbidities such as bronchopulmonary dysplasia [1, 2], sepsis [1], retinopathy of prematurity [3], necrotizing enterocolitis (NEC) [3,4], and intraventricular hemorrhage (IVH) [4–6]. While a cause-and-effect has not been established, the association between transfusions and common morbidities have prompted clinicians to re-evaluate the safety and value of RBC transfusion guidelines.

Few studies have focused on the roles transfusions and recombinant erythropoietin (Epo) play on neuronal development. It is unknown whether better cognitive outcomes are a result of neuroprotective effects of erythropoiesis stimulating agents (ESAs), improved oxygenation due to higher hematocrit in ESA recipients, increased neuronal injury or morbidity due to transfusions, a combination of these, or other factors – associations we feel deserve further study.

ESAs such as Epo and Darbepoetin alfa (Darbe) increase red cell mass and decrease transfusion requirements [7]. In our previously reported randomized controlled trial that incorporated standardized transfusion guidelines, ESA recipients received significantly fewer transfusions and were exposed to fewer donors [8]. In addition, 58% of ESA recipients did not receive a transfusion, compared to 38% in the placebo group [8]. Evaluating those infants at 18–22 months, we found that the ESA recipients had better cognitive outcomes than did the placebo recipients [9]. Developmental testing at 3.5–4 years of age continued to show better cognitive outcomes of the ESA recipients [10]. These improvements included better scores in domains of executive function: working memory, cognitive flexibility, and impulse control.

However, it is unclear whether the better cognitive outcomes were due to neuroprotective effects of ESAs, higher hematocrits in ESA recipients (8), fewer transfusion in the ESA recipients, or some combination of these factors. To more clearly understand our observed outcomes, we performed a secondary analysis of our ESA trial and correlated the transfusion number and volume each study infant received with their developmental scores at 18–22 months and 3.5–4 years. We hypothesized that transfusions and transfusion volumes would be inversely correlated with cognitive outcome.

Methods

Initial ESA Study:

Subjects: Preterm infants 500–1,250 grams birth weight were enrolled in either ESA or placebo treatment arms at ≤48 hours after birth. Randomization was stratified by center (New Mexico, Utah and Colorado) using a computer-generated permuted block method. All care givers 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 on ClinicalTrials.gov (NCT00334737).

Dosing of Study Drug and supplements: Infants were randomized to one of three groups: Epo, 400 units/kg, given subcutaneously (SC) three times a week; Darbe, 10 μg/kg, given SC once a week, with sham dosing two other times per week; or placebo, consisting of three sham doses per week. Dosing continued until 35 completed weeks gestation, discharge, transfer to another hospital, or death. All infants received supplemental iron, folate, and vitamin E.

Transfusion Guidelines: A standardized uniform transfusion protocol, based on hematocrit/hemoglobin levels and respiratory support, was used to determine when infants would be transfused (Table 1).

Developmental Follow-Up at 18–22 months

Children were evaluated at 18–22 months corrected age at the New Mexico, Utah, and Colorado sites by examiners blinded to the treatment group. The study was approved by the IRBs at the Universities of New Mexico, Utah, and Colorado, and informed consent was obtained from parents. Cognitive outcomes were assessed using the Bayley Scales of Infant Development III (BSID). Composite cognitive, language, social/emotional, and object permanence scores (a subset of the BSID evaluating executive function) were determined.

Developmental Follow up at 3.5–4 years

Children previously enrolled in this study were eligible for the BRITE Study (BRain Imaging and Developmental Follow-up of Infants Treated with Erythropoietin; NCT01207778), performed at the Utah and New Mexico sites. Because a new informed consent was required for the BRITE study, not all previous subjects were enrolled; therefore, sample size estimates were not performed. Children were evaluated at 3.5–4 years of age at the New Mexico or Utah sites by examiners who remained blinded to the treatment group. Cognitive outcomes were assessed using the Wechsler Preschool and Primary Scale of Intelligence III (WPPSI). The WPPSI test involved the administration of verbal, performance, and general language scales to calculate a Full-Scale IQ score (combination of verbal and performance scales).

Statistical Analysis

Baseline characteristics, growth, and medical outcomes were compared between ESA and placebo treatment arms using Kruskal-Wallis tests for quantitative dependent variables and

chi-squared tests for nominal and categorical dependent variables. A linear regression model (ESA and placebo recipients combined) was used to compare cognitive scores from BSID and WPPSI-III with transfusion number or volumes recorded during the initial hospital stay. We performed initial analyses to determine if there should be a sex interaction term in our model. We found that sex as an interaction term was not significant and was therefore not included. Subjects were grouped according to transfusion status: infants who received no transfusions were compared to infants who received ≥ 1 transfusion.

Results

A total of 99 infants participated in the original randomized control trial, 33 per treatment arm (Darbe, Epo, and placebo; Figure 1 online). Ninety-two infants survived to discharge. At 18–22 months of age, 80 infants were evaluated (24 placebo, 56 ESA treated). Fourteen infants were lost to follow up due to reasons including parent refusal (39%), consent not requested (5%), or enrollment in other studies (37%) [8]. At 3.5–4 years, 39 ESA-treated children and 14 placebo-treated children were evaluated. Analysis of data between those who received Epo and those who received Darbe revealed no differences in cognitive testing or transfusion exposure, thus their data were compiled into one ESA group.

Characteristics of study subjects at initial enrollment, at 18–22 months, and at 3.5–4 years are shown in Table 2. There were no differences in birth weight, gestational age, and gender between ESA and placebo groups. As published previously, infants in the placebo group received significantly more transfusions (p=0.04) and greater transfusion volumes (p=0.03) compared to infants in the ESA-treated group [8]. Twelve of 33 of the placebo recipients (36%) did not receive a transfusion during hospitalization, while 37 of 66 (56%) of ESA recipients did not receive transfusions. No infant received a transfusion following discharge from the hospital. Characteristics of study subjects at the follow up periods, shown in Table 2, revealed that the age at follow up did not differ between treatment groups. Children in the placebo group were more likely to have neurodevelopmental impairment compared to ESA-treated infants (p = 0.005 at 18–22 months and 0.007 at 3.5–4 years) [8–10].

Of those infants seen at 18–22 months, a similar percentage (compared to their hospital phase) of non-transfused infants were seen: 10 of 24 (42%) placebo recipients (compared to 36% during hospitalization) and 33 of 56 [59%] ESA recipients (compared to 56% during hospitalization). A similar percentage (compared to hospital phase and 18–22 month follow up) of non-transfused subjects were seen in each group at 3.5–4 years as well (29% placebo, 59% ESA).

At 18–22 months, red cell transfusion volumes were inversely correlated with composite cognitive scores (r= −0.26, p=0.02, Figure 2A). There was a trend toward an inverse relationship between transfusion number and cognitive scores, which did not reach statistical significance (Figure 2B, r= −0.37; p=0.077). Transfusion volumes were also inversely correlated with social/emotional scores (p=0.05; data not shown) but not language scores (p=0.22; data not shown).

Among those who received one or more transfusions, both cognitive (p=0.003) and language (p=0.03) scores were significantly higher in the ESA-treated group than the placebo group (Figure 3A and B). There were no differences in cognitive (p=0.76) or language (p=0.62) scores between ESA and placebo groups in those infants who had not received any transfusions.

At 3.5–4 years, transfusion number (p=0.5) and volume (p=0.61) did not correlate with full scale IQ (data not shown). Cognitive scores remained similar in the ESA-treated group whether infants were transfused or not (Figure 4). ESA-treated infants had significantly higher cognitive scores than placebo-treated infants (Figure 4), in those receiving no transfusions (p=0.05) and those receiving ≥1 transfusion (p=0.03).

Discussion

We evaluated the relationship between number and volume of RBC transfusions and long-term neurocognitive outcomes, among former preterm infants randomized to treatment with ESAs or placebo. Ours is the first study to report this relationship.

For all former preterm children in this study, cognitive scores at 18–22 months of age correlated inversely with red cell volume and number of transfusions received as neonates. At 4-year follow-up, this relationship was no longer apparent. However, cognitive scores at 18–22 months were significantly lower in the subset of placebo recipients who received any transfusions compared to those who remained non-transfused. Cognitive scores at 18–22 months and 3.5–4 years were similar between transfused and non-transfused infants in the ESA-treated group. Cognitive scores in the placebo group decreased at the 3.5–4 year visit, which may reflect worsening impairment in the placebo group over time that was not previously identified at 18–22 months. Thus, we speculate that transfusions might negatively impact cognitive development, and that ESAs provide neuroprotection from these negative effects.

In studies of adults by Carson et al, liberal transfusion guidelines called for administering transfusions when the hemoglobin level fell below 10 g/dL, while restrictive transfusion guidelines did not call for transfusions unless hemoglobin levels fell below 7–8 g/dL [11]. Liberal transfusion guidelines resulted in a greater number and volume of transfusions in order to maintain higher hemoglobin concentrations. In other studies of adult patients, the risk of a major infection post-transfusion increased 29% with each RBC unit transfused [12, 13]. These findings have led researchers and health professionals to discuss when and exactly how many transfusions are optimal. In adults, a restrictive transfusion strategy lowers overall hospital mortality rates, including decreasing post-transfusion myocardial infarction rates [11, 13]. Studies assessing the effect of either liberal or restrictive transfusion guidelines in adults with acute upper gastrointestinal hemorrhage, as well as those recovering from cardiac surgery, found that morbidity and mortality rates between groups were comparable [14, 15]. The results of these studies indicate that more transfusions may not be as beneficial as previously thought, especially for critically ill adults [16]. Similarly, a meta-analysis assessing RBC transfusions in adults undergoing cardiac surgery found that those who received transfusions had higher mortality rates than those who did not

receive any, supporting the idea that a restrictive transfusion strategy may be more beneficial for patients with stable cardiac disease [13].

In neonatal patients, anemia has been linked to increased intra-hospital morbidity and mortality rates. Preoperative anemia, defined as a hematocrit ≤ 40%, was a significant, independent risk factor for postoperative mortality in neonates undergoing non-cardiac surgery [17]. A hemoglobin ≤ 8 g/dL was also found to be an independent risk factor for NEC in very low birth weight infants (VLBW). Though transfusion was not found to be an independent risk factor for NEC, the same study found the incidence of NEC to be higher in infants who received RBC transfusions versus those who did not [18]. VLBW infants are at a higher risk of anemia of prematurity and therefore typically receive more transfusions than do larger infants. However, intrahospital mortality has been found to be significantly higher in VLBW receiving transfusions [2, 19]. A meta-analysis assessing transfusions in neonates suggest that there is no significant difference in morbidity and mortality rates between restrictive and liberal transfusion strategies [20].

Although preterm infants are maintained at higher hemoglobin levels in order to increase systemic oxygen transport to tissues, higher hemoglobin levels do not necessarily improve oxygen uptake [21]. In a retrospective analysis, infants maintained at lower hemoglobin levels had fewer episodes of tachycardia and apnea associated with anemia of prematurity [3]. Furthermore, studies evaluating the pathogenesis of IVH suggested that because preterm infants lack the structural support of the microvasculature in the brain, wide fluctuations in blood flow might result in rupture and hemorrhage of capillaries resulting in IVH [4–6].

In a randomized trial by Neubauer et al, neurodevelopmental impairment, defined as cognitive scores <70, blindness, deafness, or cerebral palsy was greater in the placebo group [22]. These preterm infants received the greatest number of transfusions [8]. There have been conflicting reports on the developmental outcomes of infants (not receiving ESAs) who were randomized to liberal or restrictive transfusion strategies. Kirpalani and colleagues [23] randomized 451 infants to a low or high threshold hemoglobin strategy and reported no difference in neurologic morbidities between groups; however, analyses at 2 years of age revealed increased number of infants with BSID II mental developmental index<80 in the low hemoglobin threshold group [21]. Conversely, improved cognition and brain growth were reported in the restrictively transfused group of the Iowa study by Bell and colleagues [24, 25], underscoring the need for long term evaluation and more comprehensive study. These investigators are collaborating on an ongoing NICHD Neonatal Research Network study, the Transfusion of Prematures Trial (TOP; Clinical Trials #NCT01702805). Over 1800 ELBW infants were randomized to a liberal or restrictive transfusion strategy. The primary outcome of the presence or absence of neurodevelopmental impairment at 2 years will soon be published. A similarly designed study, the Effects of Transfusion Thresholds on Neurocognitive Outcome (ETTNO) study, was recently completed [26]. Investigators showed no significant differences in cognitive outcomes among ELBW infants randomized to liberal or restrictive transfusion strategies. They concluded that a liberal blood transfusion strategy did not reduce the likelihood of death or disability at 24 months compared with a restrictive strategy.

The non-hematopoietic benefits of ESAs have been studied in clinical trials and animal models. A recent randomized control trial found that the early administration of high-dose Epo is safe in premature infants. Infants given Epo experienced no increase in mortality or morbidity, such as arterial hypertension, polycythemia, or thromboembolic events, and had significantly higher hematocrit levels compared to the placebo group [27]. Previous research in animal models found Epo receptors on astrocytes, neurons, and oligodendrocytes. Epo has been described as a neurotrophic agent, as it increases neurogenesis and oligodendrogenesis, allowing for growth of the developing brain [28–30]. Moreover, Epo has neuroprotectant and neuroreparative effects, and has anti-inflammatory actions in the central nervous system, reducing pro-inflammatory cytokine effects and thereby minimizing neuronal injury [28–30]. In contrast, RBC transfusions of preterm neonates are associated with an increase in blood concentrations of pro-inflammatory cytokines [31]. Recent clinical studies report that Epo treatment within 42 hours of birth is associated with decreased incidence of encephalopathy of prematurity, as indicated by a decrease in periventricular white matter loss and gray matter injury [29]. Epo-treated neonates also show improved white matter development that may be associated with neuronal healing [30].

The hypothesis-generating observations reported here focus on the roles transfusions and Epo play on neuronal development. It is unknown whether better cognitive outcomes are a result of neuroprotective effects of ESAs, improved oxygenation due to higher hematocrit in ESA recipients, increased neuronal injury or morbidity due to transfusions, a combination of these, or other factors – a correlation that requires further study. A major limitation of this study is that our sample size was small, although we were able to follow subjects longitudinally over a four year period. The results from the TOP trial and the ETTNO study will provide outcome data on over 2,700 extremely low birth weight infants. Based on our work, we speculate that there will be no difference in developmental outcomes between infants transfused at a higher hematocrit threshold compared to those transfused at a lower hematocrit threshold. In addition, the Epo for neuroprotection trial (PENUT; #NCT01534481) and a Neonatal Research Network trial of Darbepoetin administration to preterm infants (#NCT03169881) will provide transfusion data on over 3000 extremely low gestational age infants randomized to an ESA or placebo. Evaluating the relationship between cognitive outcomes at 2 years and transfusion number and volume (with or without the addition of ESAs) will provide significant insight into the role red cell transfusions play in the developmental outcomes of infants born prematurely.

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Abbreviations:

Darbe	darbepoetin alfa
ELBW	extremely low birth weight
Epo	erythropoietin
ESA	erythropoiesis stimulating agents
VLBW	very low birth weight
BSID-III	Bayley Scale of Infant Development III
WPPSI-III	Wechsler Preschool and Primary Scale of Intelligence III
OP	object permanence
CP	cerebral palsy
FSIQ	Full Scale IQ
PIQ	Performance IQ
VIQ	Verbal IQ

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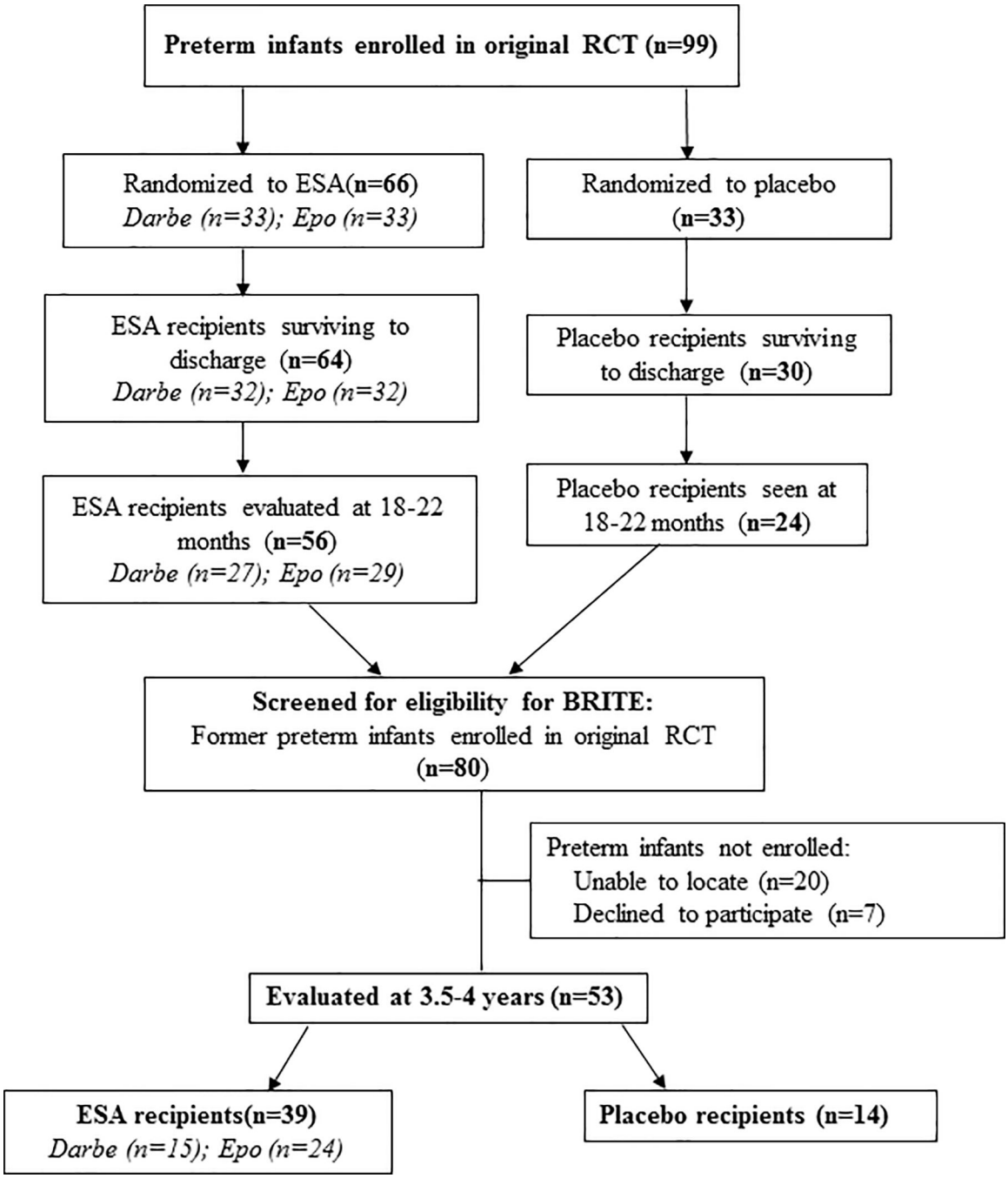

Figure 1:
Numbers of infants who were screened for eligibility, randomly assigned to receive Epo, Darbe, or placebo, and followed 18–22 months and 3.5–4 years of age.

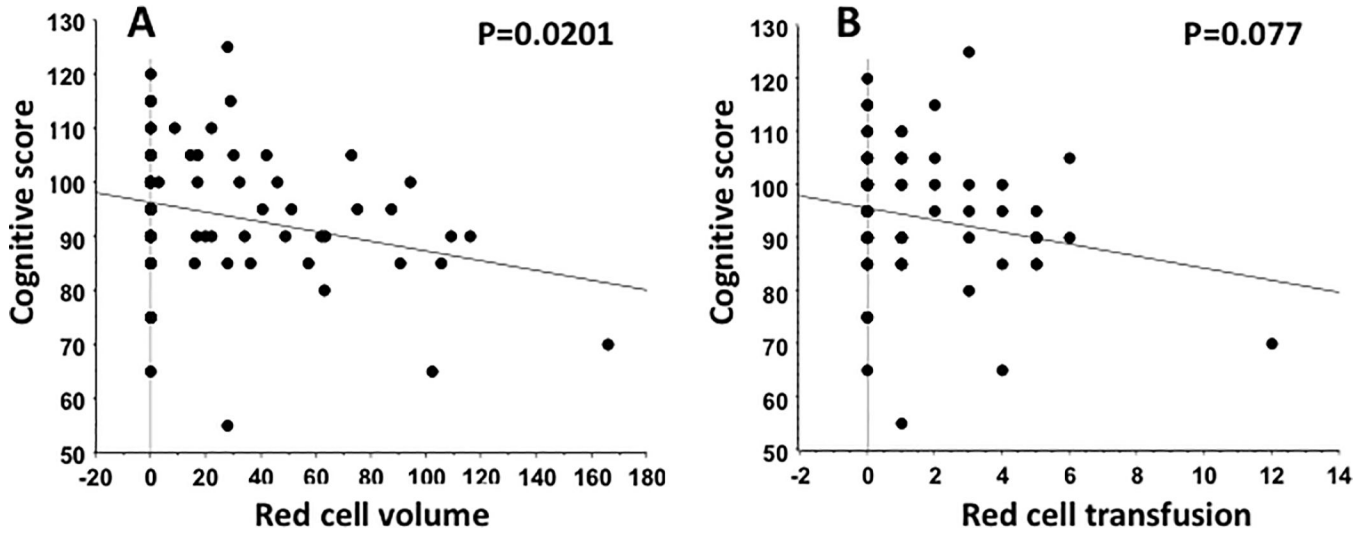

Figure 2:

Relationship between BSID-III composite cognitive scores and transfusions. (A) cognitive scores versus transfusion volume (p=0.02); (B) cognitive scores versus transfusion number (p=0.077). There was a significant inverse relationship between cognitive scores and transfusion volume.

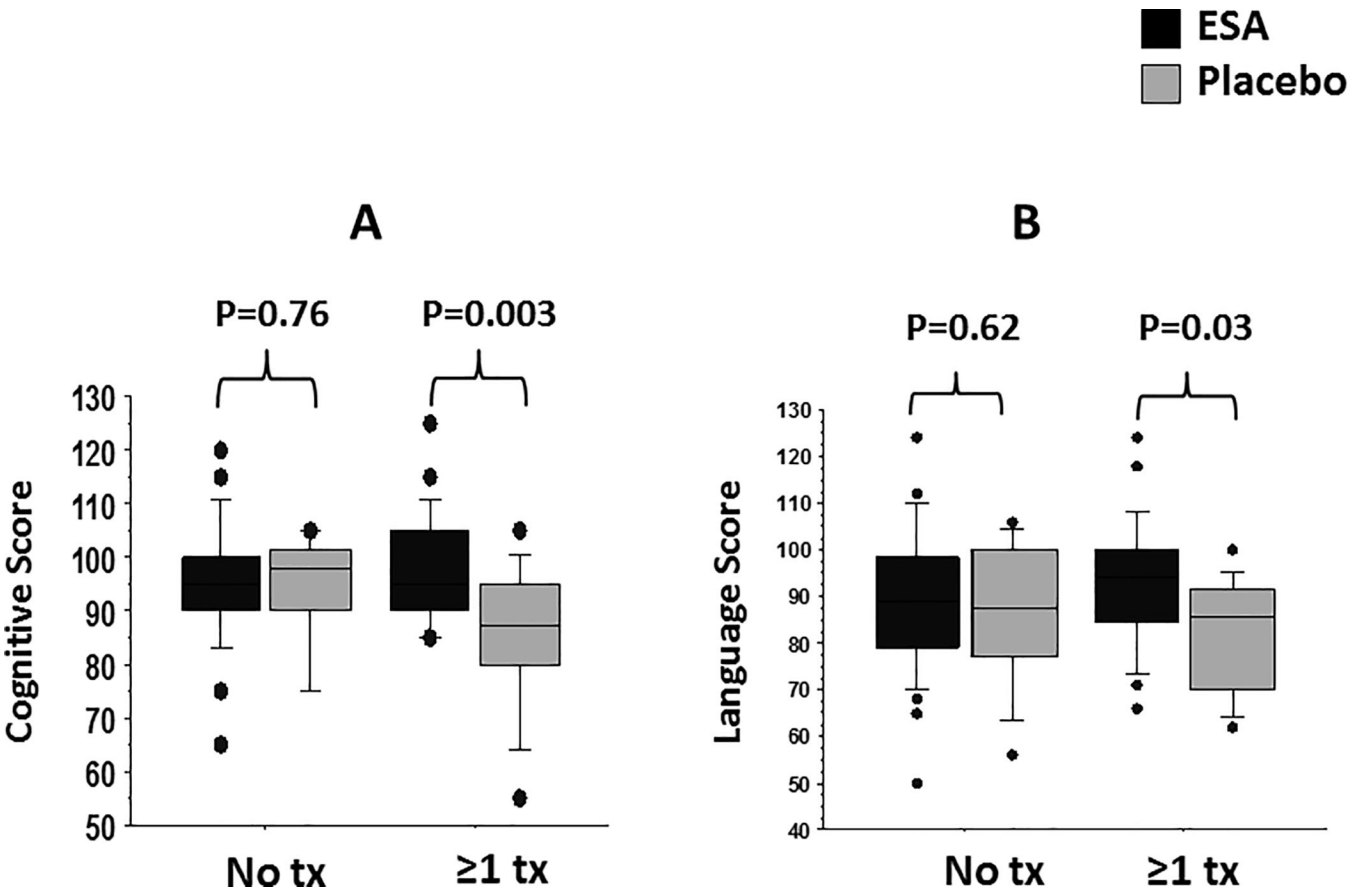

Figure 3:

Comparison of BSID-III (A) composite cognitive scores and (B) language scores at the 18–22 month follow up period between ESA-treated and placebo-treated infants; grouped by receiving either no transfusions or ≥1 transfusion. In infants receiving ≥1 transfusion, ESA-treated infants had significantly higher composite cognitive scores (0= 0.003) and language scores (p=0.03) when compared to placebo-treated infants.

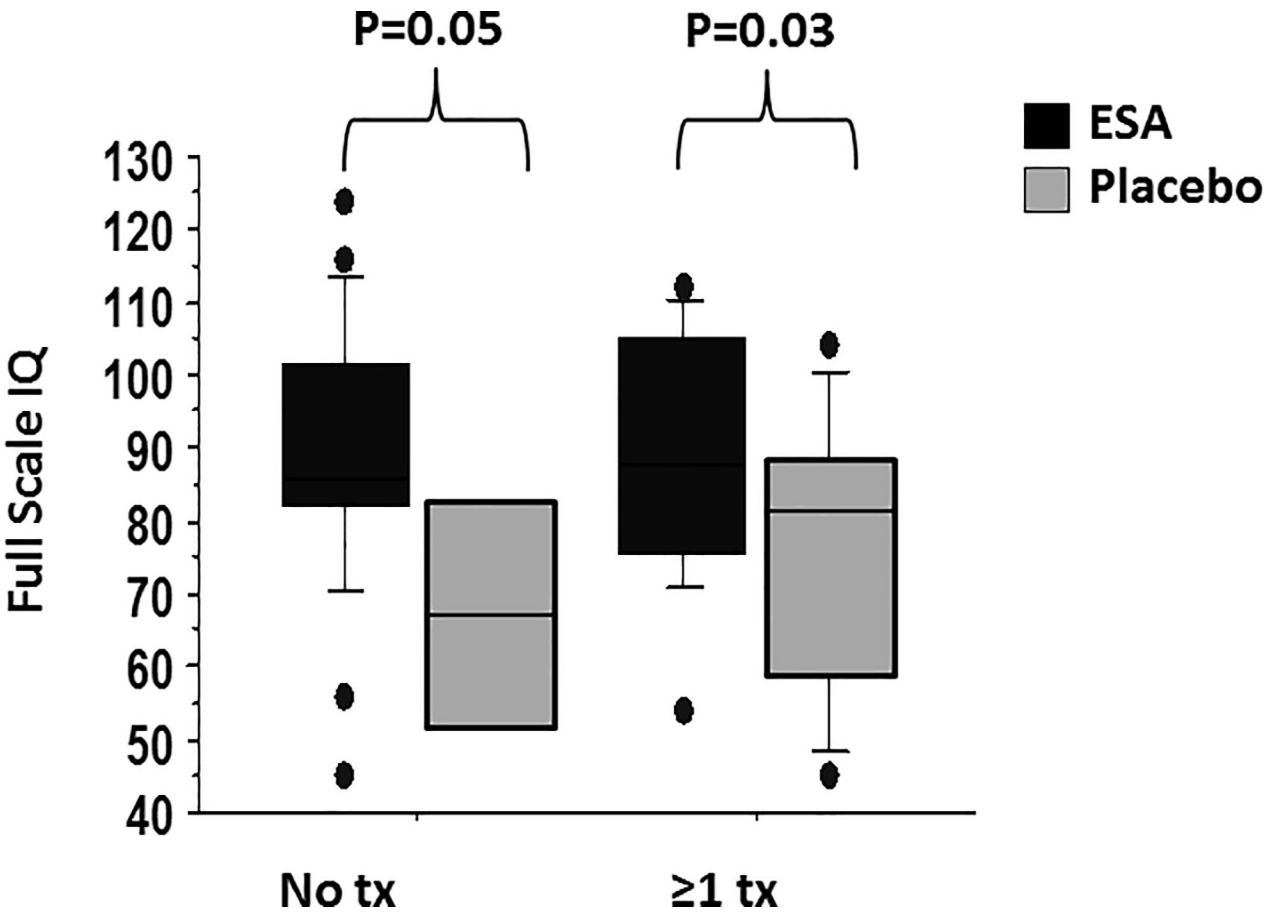

Figure 4:

Comparison of WPPSI-III Full Scale IQ (FSIQ) scores at the 3.5–4 year follow up period between ESA-treated and placebo-treated infants; grouped by receiving either no transfusions or ≥1 transfusion. By 3.5–4 years of age, there were no differences in cognition in the placebo group between those who, as infants, received transfusions and those who did not.

Table 1:

Transfusion protocol

Hematocrit/ hemoglobin	**Transfusion Volume**	**Respiratory support and/or symptoms**
30 %/10 grams/dL	15 mL/kg	moderate/significant ventilation (MAP >8 cm H_2O **AND** FiO_2 >0.4)
25%/8 grams/dL	20 mL/kg	minimal respiratory support (any mechanical ventilation with FiO2 ≤0.4, **OR** CPAP >6 cm H_2O and FiO_2 ≥0.4)
20%/7 grams/dL	20 mL/kg	supplemental oxygen **OR** CPAP with an FiO_2≤0.4, **AND** at least one of the following: • ≥24 hours of tachycardia (heart rate >180) or tachypnea (RR >60); • a doubling of the oxygen requirement from the previous 48 hours • lactate ≥2.5 mEq/L or an acute metabolic acidosis (pH<7.20); • weight gain <10 grams/kg/day over the previous 4 days while receiving ≥120 kcal/kg/day; • undergoing surgery within 24 hours
18%/6 grams/dL	20 mL/kg	Asymptomatic **AND** an absolute reticulocyte count <100,000 cells/μL

Summarized from reference 8.

Table 2.

Subject Characteristics

Initial Enrollment	**Placebo**	**ESA**	**p**
Subjects — no.	33	66	
Female — no. (%)	9 (38)	27 (48)	1.0
Birth weight (g) — median (IQR)	1005.0 (220.5)	946.0 (351.0)	0.9
Gestation (weeks) — median (IQR)	28.0 (1.2)	28.0 (2.0)	0.51
Transfusion Number — median (IQR)	3 (4)	1 (2)	0.04
Transfusion Volume — median (IQR)	53 (58)	21(32)	0.03
Hospital Morbidities:			
ROP, Stage ≥ 3 requiring intervention— no. (%)	1 (4.2)	2 (3.6)	NS
IVH, Stage ≥ 3 — no. (%)	5 (20.8)	4 (7.1)	NS
NEC — no. (%)	1 (4.2)	1 (1.8)	NS
BPD — no. (%)	14 (58.3)	37 (66)	NS
18–22 Months Follow Up	**Placebo**	**ESA**	**p**
Subjects — no.	24	56	
Age at follow up (mos.) — median (IQR)	20 (1)	21 (2)	NS
Developmental assessments:			
Composite Cognitive Score— mean (s.d.)	88.7 (13.5)	96.5 (11.2)	0.01
Composite Language Score — mean (s.d.)	83.6 (13.1)	90.7 (15.4)	0.05
Object Permanence — mean (s.d.)	2.2 (1.0)	2.6 (0.7)	0.05
Neurodevelopmental Impairment:			
Any NDI — no. (%)	10 (41.7)	7 (12.5)	0.005
Cognitive score < 70 — no. (%)	2 (8.3)	1 (1.8)	0.2
Cerebral Palsy — no. (%)	5 (20.8)	0 (0)	0.002
Hearing Impairment — no. (%)	1 (4.2)	1 (1.8)	NS
Visual Impairment — no. (%)	1 (4.2)	2 (3.6)	NS
3.5–4 Year Follow Up	**Placebo**	**ESA**	**p**
Subjects — no.	14	39	
Age at follow up (mos.) — median (IQR)	48 (3)	49 (40)	NS
Developmental assessments:			
Full-scale IQ— mean (s.d.)	78.9 (18.9)	91.1 (17.5)	0.036
Performance IQ— mean (s.d.)	79.5 (19.5)	93.0 (17.0)	0.018
Verbal IQ— mean (s.d.)	82.9 (16.9)	91.7 (18.3)	0.091
Neurodevelopmental Impairment:			
Any NDI — no. (%)	6 (43)	3 (8)	0.007
Full-scale IQ < 70 — no. (%)	4 (29)	3 (8)	0.070
Cerebral Palsy — no. (%)	3 (21)	0 (0)	0.016
Hearing Impairment — no. (%)	0 (0)	0 (0)	NS
Visual Impairment — no. (%)	0 (0)	0 (0)	NS

Data are reported as median (first-third interquartile range), or percent. Data compiled from references [8] and [9]. ROP: Retinopathy of prematurity; IVH: Intraventricular hemorrhage; NEC: necrotizing enterocolitis; BPD: bronchopulomonary dysplasia; NDI: neurodevelopmental impairment