

High-dose Erythropoietin and Hypothermia for Hypoxic-Ischemic Encephalopathy: A Phase II Trial

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abstract

OBJECTIVE: To determine if multiple doses of erythropoietin (Epo) administered with hypothermia improve neuroradiographic and short-term outcomes of newborns with hypoxic-ischemic encephalopathy.

METHODS: In a phase II double-blinded, placebo-controlled trial, we randomized newborns to receive Epo (1000 U/kg intravenously; $n = 24$) or placebo ($n = 26$) at 1, 2, 3, 5, and 7 days of age. All infants had moderate/severe encephalopathy; perinatal depression (10 minute Apgar <5, pH <7.00 or base deficit ≥ 15 , or resuscitation at 10 minutes); and received hypothermia. Primary outcome was neurodevelopment at 12 months assessed by the Alberta Infant Motor Scale and Warner Initial Developmental Evaluation. Two independent observers rated MRI brain injury severity by using an established scoring system.

RESULTS: The mean age at first study drug was 16.5 hours (SD, 5.9). Neonatal deaths did not significantly differ between Epo and placebo groups (8% vs 19%, $P = .42$). Brain MRI at mean 5.1 days (SD, 2.3) showed a lower global brain injury score in Epo-treated infants (median, 2 vs 11, $P = .01$). Moderate/severe brain injury (4% vs 44%, $P = .002$), subcortical (30% vs 68%, $P = .02$), and cerebellar injury (0% vs 20%, $P = .05$) were less frequent in the Epo than placebo group. At mean age 12.7 months (SD, 0.9), motor performance in Epo-treated ($n = 21$) versus placebo-treated ($n = 20$) infants were as follows: Alberta Infant Motor Scale (53.2 vs 42.8, $P = .03$); Warner Initial Developmental Evaluation (28.6 vs 23.8, $P = .05$).

CONCLUSIONS: High doses of Epo given with hypothermia for hypoxic-ischemic encephalopathy may result in less MRI brain injury and improved 1-year motor function.

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WHAT'S KNOWN ON THIS SUBJECT: Infants with hypoxic-ischemic encephalopathy suffer a high rate (>40%) of death or moderate to severe disability, even after therapeutic hypothermia. High-dose erythropoietin reduces brain injury and improves neurologic function in animal models of neonatal hypoxic-ischemic brain injury.

WHAT THIS STUDY ADDS: Among infants undergoing hypothermia for moderate/severe hypoxic-ischemic encephalopathy, multiple high doses of erythropoietin (1000 U/kg) given intravenously over 7 days appeared safe, resulted in less MRI brain injury, and led to improved short-term motor outcomes.

To cite: Wu YW, Mathur AM, Chang T, et al. High-dose Erythropoietin and Hypothermia for Hypoxic-Ischemic Encephalopathy: A Phase II Trial. *Pediatrics*. 2016;137(6):e20160191

Perinatal hypoxic-ischemic encephalopathy (HIE), an important cause of neonatal encephalopathy, occurs in 1 to 3 per 1000 term births^{1,2} and accounts for 22% of neonatal deaths worldwide.³ Up to 12 000 infants are affected each year in the United States. Although therapeutic hypothermia provides modest improvements in outcome,⁴⁻⁸ >40% of infants who received this therapy in clinical trials either died or suffered moderate to severe disabilities, including cerebral palsy, intellectual impairment, and epilepsy.⁵⁻⁹ Adjuvant neuroprotective therapies are needed to further improve outcomes after HIE.

Erythropoietin (Epo) is a cytokine that demonstrates remarkable neuroprotective and neuroregenerative effects in the brain.¹⁰⁻¹⁵ In a phase I trial of combined Epo treatment with hypothermia, we found that Epo (1000 U/kg given intravenously) provided the optimal plasma Epo levels consistent with animal studies of neuroprotection.¹⁶ Although the study was not designed to evaluate efficacy, patients who received multiple high doses of Epo exhibited a lower rate of death or moderate/severe disability at 22 months (4.5%)¹⁷ than had been expected based on studies of infants with similar entry criteria who received hypothermia alone (44%–51%).^{4-6,8}

Two small trials in China and Egypt found that Epo therapy improved short-term neurologic outcomes after HIE.^{18,19} However, these trials used alternative dosing regimens and did not include the use of hypothermia. In countries where therapeutic hypothermia has become a standard of care,²⁰⁻²² novel neuroprotective agents should be evaluated together with hypothermia.²³ Epo is commercially available, easy to administer, and has a good safety profile in newborns.²⁴ To further evaluate Epo as a potential neuroprotective agent for HIE, we

TABLE 1 Severity of Encephalopathy, Based on Modified Sarnat Scoring System

	Moderate	Severe
Consciousness	Decreased	Absent
Spontaneous activity	Decreased	No activity
Tone	Hypotonia	Flaccid
Suck	Weak	Absent
Moro	Incomplete	Absent
Respiration	Periodic breathing	Apnea

Encephalopathy = at least 3 of 6 criteria present. Severe = more symptoms in the severe than moderate column. Moderate = more symptoms in the moderate column. If encephalopathy signs were equally distributed between moderate and severe categories, severity of encephalopathy was based on level of consciousness.⁴

performed a phase II trial to compare early developmental outcomes in patients treated with Epo plus hypothermia with those who received hypothermia alone.

METHODS

In a multicenter, double-blinded, placebo-controlled trial (Neonatal Erythropoietin and Therapeutic Hypothermia Outcomes, or “NEATO”), we enrolled 50 newborns with moderate/severe HIE at 7 centers: Children’s National Health System ($n = 9$); University of California, San Francisco ($n = 9$); Seattle Children’s Hospital ($n = 8$); Arkansas Children’s Hospital ($n = 8$); Washington University, St Louis ($n = 8$); Stanford University ($n = 6$); and Kaiser Permanente Santa Clara ($n = 2$). The study received institutional review board approval at all hospitals, was overseen by an independent data and safety monitoring board (DSMB), and was registered with the US Food and Drug Administration (Investigational New Drug 102 138).

Patient Selection

Participants met 4 inclusion criteria: (1) ≥ 36 weeks gestational age; (2) whole-body hypothermia ($n = 42$) or selective head cooling ($n = 8$) initiated by 6 hours of age; (3) perinatal depression with at least 1 of the following: 10 minute Apgar score < 5 ; need for chest compressions or endotracheal/mask ventilation at 10 minutes; pH < 7.00 or base deficit ≥ 15

in cord or arterial blood within 60 minutes of birth; and (4) moderate/severe encephalopathy evident by at least 3 of 6 modified Sarnat criteria present between 1 to 6 hours of age, as defined in Table 1.^{4,6,25} We evaluated severity of encephalopathy at baseline and at 5 and 7 days of age.

We excluded patients with any of the following: age at time of consent > 23.5 hours; congenital anomaly; suspected genetic syndrome; birth weight < 1800 g; head circumference < 2 SDs below the mean; no indwelling line; withdrawal of care being considered because of moribund condition; or unlikely to obtain follow-up at 12 months of age.

Intervention

After consent was obtained, participants were randomized to receive either Epo (1000 U/kg intravenously) or an equal volume of normal saline on days 1, 2, 3, 5, and 7. The first study drug dose was given as soon as possible, up to 24 hours of age. Pharmacists assigned participants to treatment groups by using a randomization table created by a biostatistician. Randomization was stratified by site and severity of encephalopathy. All participants, study personnel other than pharmacists and biostatisticians, and all outcome assessors were blinded to treatment assignment.

Neurodevelopmental Outcome

Primary outcome was determined a priori to be 12-month neurodevelopment assessed by

(1) Alberta Infant Motor Scale (AIMS),^{26–30} a standardized and validated exam that objectively rates motor function, and (2) the Warner Initial Developmental Evaluation (WIDEA), a 43-item parental questionnaire that assesses 4 domains of infant development: self-care, mobility, communication, and social cognition.^{31,32} The WIDEA was also administered at 6 months of age. Moderate to severe neurodevelopmental impairment at 12 months was defined as an AIMS score less than the fifth percentile for age, or a WIDEA score >2 SDs below the mean based on normative data from typically developing infants at 12.9 months of age (ie, WIDEA <76.4).³³ All AIMS and WIDEA evaluators underwent centralized training to maximize consistency across sites.

Safety

Serious adverse events required expedited review by an independent DSMB: (1) in-hospital death; (2) severe cardiopulmonary collapse requiring cardiopulmonary resuscitation within 2 hours of study drug; (3) thrombosis of a major vessel; or (4) unexpected events thought to be related to the study drug. We also recorded adverse events that are frequent comorbidities of HIE: disseminated intravascular coagulation with clinical bleeding requiring transfusion; hypotension requiring inotrope or vasopressor support; hypertension requiring antihypertensive medication; liver injury (alanine aminotransferase >100 IU/L); persistent pulmonary hypertension requiring nitric oxide and fraction of inspired oxygen >0.50; platelet count <100 000 per μ L; creatinine >1.5 mg/dL; sepsis (positive blood culture and at least 7 days of antibiotic treatment); and polycythemia requiring intervention.

Neuroimaging

Neonatal brain MRI was performed as part of routine clinical care at 4 to 7 days of age. This time window minimizes the likelihood of diffusion-weighted imaging pseudonormalization, and follows the American Academy of Neurology practice parameters.^{34–36} Two central reviewers (R.M. and A.M.), who were blinded to treatment allocation, independently scored brain MRI findings as previously described,³⁴ resolving discrepancies through discussion. Global brain injury score (range, 0–138) was determined by measuring injury severity (0 = normal, 3 = severe) in 8 brain regions in each hemisphere (caudate, putamen/globus pallidus, thalamus, posterior limb of internal capsule, white matter, cortex, brainstem, and cerebellum) and adding these component scores together.³⁴ Severity of brain injury was categorized as “none” = 0; “mild” = 1–11; “moderate” = 12–32; or “severe” = 33–138.

Statistical Analyses

For primary analysis of treatment effect, we used an intention-to-treat strategy. We calculated the effect of Epo on developmental outcome measures, 95% confidence intervals, and corresponding *P* values (significance, *P* < .05) by using a linear regression with robust SEs, with and without adjusting for age at testing and for severity of encephalopathy at baseline. We compared categorical variables between randomized treatment groups by using a χ^2 test, or Fisher’s exact test when the count was ≤ 5 . To compare baseline continuous variables between treatment groups, we performed a two-sided *t* test with unequal variances, and a Wilcoxon rank sum test for the global brain injury score because these data were right-skewed. We used a Poisson regression model with robust SEs adjusting for severity of

encephalopathy to compare adverse event and serious adverse event counts between treatment groups. The sample size was determined to provide sufficient evidence regarding the equivalence or noninferiority of Epo relative to the placebo for key safety measures, with 50 subjects yielding 80% power to evaluate equivalence when using tolerance limits of 0.5 SDs for quantitative measures of organ function. The sample size of 50 was also considered adequate to evaluate feasibility for a future phase III trial. Neuroimaging biomarkers were explored as secondary outcomes, and thus no corrections were made for multiple comparisons. All statistical analyses were performed by an independent biostatistician by using R statistical software (version 3.2, The R Foundation, Vienna, Austria).³⁷ All reported *P* values are 2-sided.

RESULTS

Of 154 newborns with HIE who were evaluated from January to November 2012, 81 (53%) were eligible and 68 were approached for consent (Fig 1). Fifty (74% consent rate) were randomly allocated to receive Epo with hypothermia (*n* = 24) or hypothermia alone (*n* = 26). The first study drug dose was administered at a mean age of 16.5 hours (SD, 5.9). Forty (80%) infants received all 5 doses; the remaining 10 did not because they died before completing treatment (*n* = 5), lost intravenous access (*n* = 3), or were discharged to home before 7 days (*n* = 2). Of the 24 infants in the Epo group, 22 (92%) received all 5 doses, 1 (4%) received 4 doses, and 1 (4%) only received 1 dose due to redirection of care.

The 2 treatment groups were similar with respect to baseline characteristics (Table 2), except for a higher frequency of large for gestational age infants in the Epo group (25% vs 4%, *P* = .04). All infants were singleton gestation.

Severity of encephalopathy was not significantly different between the groups.

Neonatal Outcomes

Death during neonatal hospitalization occurred in 7 (14%) patients, and did not differ significantly between treatment groups (8% vs 19%, $P = .42$). Death was more common after severe encephalopathy compared with moderate encephalopathy (44% vs 7%, $P = .02$). All deaths were attributed to redirection of care due to critical medical condition ($n = 3$), poor neurologic prognosis ($n = 1$), or both ($n = 3$). Moderate/severe encephalopathy based on Sarnat exam had resolved by 5 days in a larger proportion of infants treated with Epo than those treated with the placebo (61% vs 32%, $P = .045$); this difference was no longer significant at 7 days (67% vs 48%, $P = .13$).

Neurodevelopmental Outcome

Forty-one (82%) subjects survived and underwent a 12-month evaluation (Fig 1). Of 43 survivors, 41 (95%) were successfully evaluated at a mean age of 12.7 months (SD, 0.9). Age at follow-up did not differ between treatment groups (Table 3). No patients died between hospital discharge and final follow-up. At 12 months, the AIMS evaluation revealed a significantly higher score in the Epo group compared with the placebo group (53.5 vs 42.8, $P = .02$), whereas the WIDEA score showed a trend toward improvement in the Epo group (122 vs 110, $P = .10$). The 6-month WIDEA score was higher in the Epo group (75.3 vs 68.8, $P = .04$). After adjusting for age at testing and severity of encephalopathy, these differences did not appreciably change (Table 3).

Additional exploratory analyses were conducted, but not corrected for multiple comparisons because they were not considered confirmatory endpoints in this phase II trial. The WIDEA mobility subscore was higher

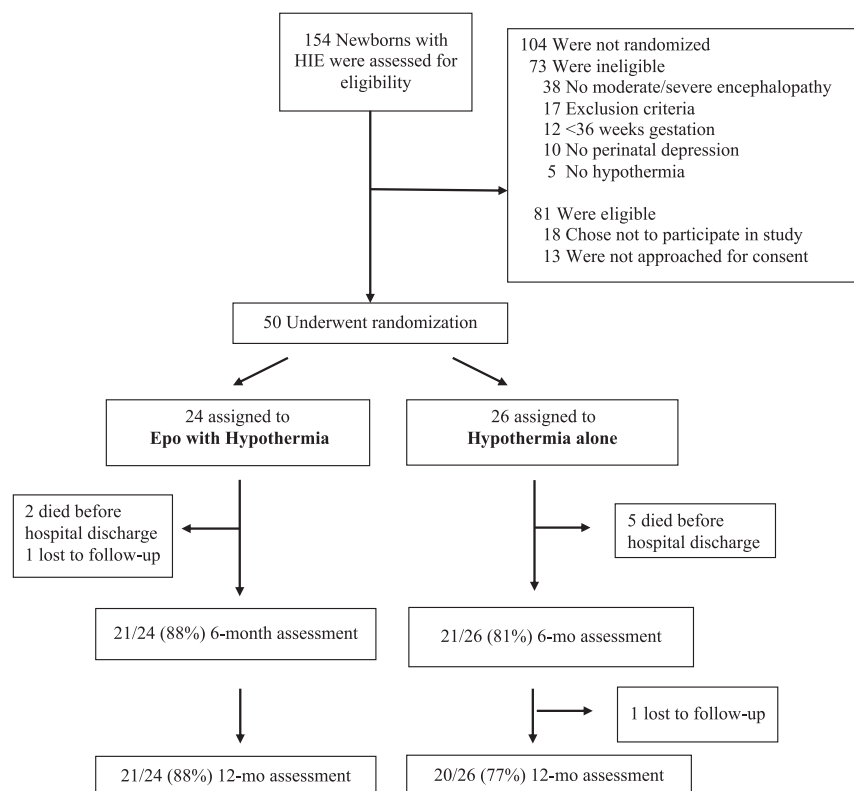


FIGURE 1
Evaluated newborns with HIE.

in the Epo group at 12 months (28.6 vs 23.8, adjusted $P = .048$). When comparing the composite outcome of death or moderate to severe neurodevelopmental impairment at 12 months in Epo and placebo groups (16.7% vs 38.5%, $P = .12$), there was a nonsignificant trend toward benefit with treatment.

Safety

No adverse events were attributed to Epo. Expected adverse events were common and evenly distributed (Table 4), except for a higher rate of sepsis in the placebo group. No patients in either group developed polycythemia. The mean, final hematocrit recorded at a mean age of 5.7 days did not differ between the Epo and placebo groups (37.1 vs 38.4, $P = .53$).

Serious adverse events occurred in 9 patients, and were seen in both treatment groups (Table 4). In addition to the 7 hospital deaths, 1

patient in each group developed a deep vein thrombosis, and 1 infant required cardiac compressions and intubation within 2 hours of receiving Epo; however, the cardiopulmonary compromise was in the setting of severe multiorgan injury and was considered by the DSMB to be unlikely related to the study drug.

Neuroimaging

Brain MRI was performed in 48 (96%) infants at a mean age of 5.2 days (SD, 2.2). Two patients died before neuroimaging was obtained. Of the 23 patients in the Epo group who had a brain MRI, all had received at least 3 doses of the study drug before undergoing neuroimaging. Global brain injury score on MRI ranged from 0 to 70 (interquartile range [IQR], 1–11). Infants who received Epo had significantly lower global brain injury scores (median, 2; IQR, 0–8.5) than those in the placebo

TABLE 2 Baseline Characteristics of Study Participants by Treatment Group

Baseline Characteristics	Epo (n = 24)		Placebo (n = 26)		P ^a
	n	n (%)	n	n (%)	
Maternal race	24		26		.49
White		14 (58)		18 (69)	
Black		7 (29)		4 (15)	
Asian		2 (8)		1 (4)	
Other		1 (4)		3 (12)	
Maternal Hispanic ethnicity	24	5 (20.8)	26	6 (23.1)	.85
Maternal age, mean (SD)	24	29.4 (7.2)	26	29.7 (6.6)	.87
Maternal education	21		24		.82
High school or less		10 (47)		10 (42)	
Some college or university		5 (24)		7 (29)	
College graduate, or post-graduate		6 (29)		7 (29)	
Female infant	24	14 (58)	26	10 (39)	.26
Birth weight, g, mean (SD)	24	3556 (618)	26	3243 (512)	.06
Gestational age, wks, mean (SD)	23	38.7 (1.9)	26	38.7 (1.6)	.99
Large for gestational age	24	6 (25)	26	1 (4)	.04
Severe Sarnat encephalopathy ^b	24	5 (21)	26	4 (15)	.72
5 min Apgar	23		25		.74
0–3		11 (48)		14 (56)	
4–6		10 (43)		10 (40)	
7–10		2 (9)		1 (4)	
10 min Apgar	21		25		.39
0–3		5 (24)		7 (28)	
4–6		13 (62)		11 (44)	
7–10		3 (14)		7 (28)	
Resuscitation >10 min ^c	24	21 (88)	26	21 (81)	.70
Chest compressions	24	8 (33)	26	11 (42)	.72
Lowest pH ^d , mean (SD)	20	6.9 (0.2)	24	7.0 (0.2)	.47
aEEG severe abnormal background ^e	22	7 (32)	24	7 (29)	.85
Delivery mode	24		26		.50
Spontaneous vaginal		5 (21)		9 (34)	
Vacuum or forceps		1 (4)		2 (8)	
Elective cesarean		1 (4)		0 (0)	
Emergency cesarean		17 (71)		15 (58)	
Maternal chorioamnionitis	24	4 (17)	26	3 (12)	.70
Sentinel event ^f	24	7 (29)	26	7 (27)	.86
Age at randomization, h, mean (SD)	24	13.3 (6.1)	24	14.6 (6.1)	.48
Age at first study drug, h, mean (SD)	24	15.6 (5.7)	26	17.2 (6.1)	.35

^a P values for categorical variables are based on 2-sided χ^2 or Fisher's exact test as appropriate. For continuous variables, P values are based on 2-sided t test with unequal variances.

^b Severe encephalopathy as defined in Table 1.

^c Required ongoing resuscitation with chest compressions and/or mechanical ventilation at 10 min of age.

^d Lowest pH among cord arterial, cord venous, and arterial blood gas samples taken before 60 min of age.

^e Severe amplitude-integrated electroencephalography (aEEG) background at baseline, defined as burst suppression, continuous low voltage, or inactive flat tracing.

^f Sentinel event = placental abruption, shoulder dystocia, uterine rupture, or prolapsed cord.

group (median, 11; IQR, 4–18, $P = .01$; Table 5). Fewer Epo-treated infants had moderate to severe brain injury on MRI (4% vs 44%, $P = .002$). There was a trend toward more normal brain MRIs among patients who received Epo (35% vs 12%, $P = .09$). Injury to subcortical regions of the brain (ie, basal ganglia, thalamus, or posterior limb of the internal capsule) was significantly less common in the Epo than in the placebo group (30% vs 68%, $P = .02$). Cerebellar injury was also less

common in the Epo group (0% vs 20%, $P = .051$).

Sensitivity Analyses

Infant birth weight differed between the treatment groups ($P = .06$, Table 2); when adjusted for birth weight, the effect of treatment on MRI global injury score and on neurodevelopmental outcomes did not appreciably change. After randomization, 2 patients in the placebo group were diagnosed with conditions that would have

excluded them from the study (ie, myotonic dystrophy and brainstem malformation). When we excluded these patients from the analyses, the mean increases in the 12-month AIMS (6.8, $P = .09$) and WIDEA (5.3, $P = .42$) scores associated with Epo treatment were not statistically significant; however, the significant effect of treatment on MRI global injury score remained unchanged. None of the WIDEA or AIMS scores showed treatment moderation by gender.

TABLE 3 Neurodevelopmental Outcomes and Growth at 6 and 12 mo of Age

Outcome	Epo	Placebo	Adjusted Treatment Effect (95% Confidence Interval) ^a	<i>P</i> ^a
6 mo	<i>n</i> = 21	<i>n</i> = 21		
WIDEA				
Age at testing, mo	6.3 (0.6) ^b	6.1 (0.4)	NA	.34 ^c
Total score	75.3 (9.1)	68.8 (10.7)	6.7 (0.69 to 12.8)	.04
Self-care	28.1 (4.2)	26.1 (4.7)	1.8 (−0.97 to 4.6)	.20
Mobility	14.1 (2.7)	12.4 (2.7)	1.5 (0.07 to 3.00)	.06
Communication	16.4 (3.2)	15.3 (2.8)	1.2 (−0.63 to 3.1)	.20
Social	16.7 (4.5)	14.9 (3.2)	2.1 (−0.12 to 4.3)	.09
12 mo	<i>n</i> = 21	<i>n</i> = 20		
WIDEA				
Age at testing, mo	12.7 (0.9)	12.6 (0.9)	NA	.71 ^c
Total score	122 (14)	110 (31)	10.8 (−2.8 to 24.5)	.15
Self-care	36.7 (5.1)	33.8 (7.7)	2.8 (−1.1 to 6.8)	.18
Mobility	28.6 (3.8)	23.8 (8.9)	4.4 (0.46 to 8.37)	.048
Communication	28.2 (5.1)	25.5 (8.8)	2.2 (−1.9 to 6.3)	.33
Social	28.8 (6.4)	26.9 (8.9)	1.4 (−3.1 to 5.9)	.57
AIMS	53.5 (5.2)	42.8 (19.3)	10.2 (1.9 to 18.5)	.03
Moderate to severe NDI ^d , <i>n</i> (%)	2 (8)	5 (19)	NA	.42
Weight, kg	9.9 (1.4)	9.7 (1.2)	0.06 (−0.74 to 0.86)	.88
Height, cm	74.3 (3.2)	71.7 (6.2)	2.2 (−0.81 to 5.3)	.17
Head circumference, cm	45.7 (1.6)	45.5 (2.1)	0.2 (−1.0 to 1.4)	.75

^a Treatment effect comparing Epo to Placebo is based on linear regression adjusted for age at testing and severity of encephalopathy. 95% confidence intervals and corresponding 2-sided *P* values are based on robust (sandwich) SEs.

^b Measurements are provided as mean (SD).

^c *P* values for differences in age at testing are based on a *t* test of difference in means with unequal variances.

^d Moderate to severe neurodevelopmental impairment (NDI) among survivors at age 12 mo, defined as AIMS less than fifth percentile for age, or WIDEA <2 SDs below the mean. *P* value is based on Fisher's exact test.

TABLE 4 Adverse Events and Significant Adverse Events by Treatment Group

	Epo (<i>n</i> = 24)	Placebo (<i>n</i> = 26)	<i>P</i> ^a
Adverse events, <i>n</i> (%)			
Liver dysfunction (alanine aminotransferase >100 IU/L)	10 (42%)	6 (23%)	.16
Hypotension (requiring inotrope or vasopressor)	9 (38%)	12 (46%)	.74
Thrombocytopenia (platelet <100 000 per μ L)	6 (25%)	10 (39%)	.31
Persistent pulmonary hypertension	5 (21%)	4 (15%)	.89
Disseminated intravascular coagulation	3 (13%)	5 (19%)	.70
Sepsis (positive blood culture and antibiotics \geq 7 d)	0 (0%)	5 (19%)	.051
Renal dysfunction (creatinine >1.5)	4 (17%)	5 (19%)	.81
Hypertension (requiring antihypertensive)	1 (4%)	0 (0%)	.48
Polycythemia (requiring intervention)	0 (0%)	0 (0%)	.99
Total adverse events, <i>n</i> (<i>n</i> per patient)	38 (1.6)	47 (1.8)	.51 ^b
Patients with \geq 1 adverse event, <i>n</i> (%)	17 (71%)	16 (62%)	.49
Serious adverse events, <i>n</i> (%)			
Death during birth hospitalization	2 (8%)	5 (19%)	.42
Cardiopulmonary collapse within 2 h of drug	1 (4%)	0 (0%)	.48
Thrombosis of major vessel	1 (4%)	1 (7%)	.99
Unexpected event related to study drug	0 (0%)	0 (0%)	.99
Any of the above	3 (13%)	6 (23%)	.47
Total serious adverse events, <i>n</i> (<i>n</i> per patient)	4 (0.17)	6 (0.23)	.43 ^b

^a *P* values are based on 2-sided χ^2 or Fisher's exact test as appropriate.

^b *P* values are based on robust SEs using a Poisson regression of counts on treatment, adjusting for encephalopathy severity.

DISCUSSION

In this phase II multicenter, double-blinded controlled trial, we found that infants with moderate/severe HIE who received Epo as an adjunctive therapy to hypothermia

demonstrated reduced severity of brain injury on neonatal MRI, and improved short-term motor outcomes. Our results suggest that treatment with multiple high doses of Epo, combined with hypothermia,

is feasible, safe, and may provide further neuroprotection for moderate/severe HIE. This study also demonstrates the feasibility of performing a multicenter neonatal neuroprotection trial with a high rate

TABLE 5 Neonatal Brain MRI Findings by Treatment Group

Outcome	Epo (n = 23)	Placebo (n = 25)	P ^a
Age at MRI, days, mean (SD)	5.6 (2.8)	4.9 (1.4)	.28
Number of doses before MRI, mean (SD)	3.7 (0.8)	3.4 (0.8)	.25
Global brain injury score, n (%)			.01
None, 0	8 (35%)	3 (12%)	
Mild, 1–11	14 (61%)	11 (44%)	
Moderate, 12–31	0 (0%)	6 (24%)	
Severe, ≥32	1 (4%)	5 (20%)	
Median [IQR]	2 [0–9]	11 [4–18]	.01 ^b
Mean (SD)	5.26 (9.9)	16.36 (18.3)	
Presence of brain injury, by region ^c			
Subcortical ^d	7 (30%)	17 (68%)	.02
Cortical	4 (17%)	9 (36%)	.26
White matter	12 (52%)	15 (60%)	.80
Brainstem	1 (4%)	4 (16%)	.35
Cerebellar	0 (0%)	5 (20%)	.051
≥2 regions injured	7 (30%)	14 (56%)	.14

^a P values for categorical variables are based on 2-sided χ^2 or Fisher's exact test as appropriate.

^b P value is based on a Wilcoxon rank sum test.

^c For each region, brain injury was considered to be present if the MRI injury subscore for that region was >0.

^d Subcortical injury includes injury to the basal ganglia, thalamus, or posterior limb of the internal capsule.

of follow-up (ie, 95% of survivors) at 1 year.

Epo receptors are expressed in the brain on numerous cell types including neuronal progenitors,³⁸ mature neurons,³⁹ astrocytes,⁴⁰ oligodendrocytes,⁴⁰ and microglia.⁴¹ Epo exhibits antiapoptotic and antiinflammatory effects acutely after neonatal brain injury^{42–46} and promotes neurogenesis, plasticity, and tissue remodeling after hypoxia-ischemia.^{15,47–50} In animal models of neonatal stroke, Epo increases proliferation, migration, and differentiation of neuronal precursors, resulting in increased neurogenesis in the injured basal ganglia and cortex.^{47,51,52}

Although therapeutic hypothermia has improved the outlook of infants with HIE,^{53,54} there remains a pressing need for neuroprotective therapies that will further reduce the high rate of neurologic disabilities.^{55–57} We reported the safety and pharmacokinetics of high-dose Epo when given together with hypothermia.^{16,17} Darbepoetin, a long-acting formulation of Epo, has also been shown to be safe in newborns undergoing hypothermia for HIE.⁵⁸ Epo monotherapy, without hypothermia, may be useful for

neonatal conditions other than HIE, such as perinatal stroke,⁵⁹ congenital heart disease,⁶⁰ and brain injury of prematurity.^{61–64}

This is the first clinical study of HIE that assesses biomarkers of efficacy to evaluate whether Epo provides additional neuroprotection to hypothermia. We found that Epo treatment was associated with significantly reduced severity of brain injury on MRI, specifically in the subcortical region (ie, the area that contains the basal ganglia, thalamus, and internal capsule). In term infants, the subcortical region of the brain exhibits selective neuronal vulnerability to hypoxia-ischemia.⁶⁵ Thus, our findings suggest that Epo specifically reduces injury to the areas of the brain that are most susceptible to HIE.

Subcortical brain injury is associated with a particularly high risk for later motor disability.^{66,67} Because the Epo group had a lower incidence of subcortical injury on brain MRI, it is not surprising that Epo treatment also resulted in improved motor outcomes. Although our study was not designed to evaluate long-term outcomes, such as cerebral palsy, Epo resulted in improved short-term biomarkers of motor outcome,

as measured by observed motor evaluation (AIMS) and parental questionnaire (WIDEA) at 12 months. What constitutes a clinically significant difference in these scores at 12 months is not well established. However, the average difference in AIMS motor scores between the Epo and placebo groups (ie, 10.2 points) is equal to more than one-half of 1 SD of the scores in the placebo group (ie, 19.3 points), suggesting a relatively large effect size.

Epo may improve neurologic outcomes by acutely reducing the degree of brain injury after hypoxia-ischemia, by improving repair through its long-term effects on neuronal regeneration, or both.^{43,68} In our study, early brain MRI performed at a mean age of 5 days detected a significantly reduced amount of injury among infants who had received ≥3 doses of Epo. Furthermore, at 5 days of age, moderate/severe encephalopathy had resolved in a greater proportion of infants receiving ≥3 doses of Epo. Thus, our findings suggest that Epo exerts an acute neuroprotective effect when given in high doses during the first 3 days after birth. Animal studies have found that Epo administered in a delayed fashion

enhances brain repair.^{15,69} Whether later doses of Epo given to infants with HIE on days 5 and 7 exert additional neuroprotection remains to be determined.

The risk of serious and expected adverse events did not differ significantly between the 2 treatment groups. No patients developed polycythemia, which is consistent with the frequent phlebotomy required to treat such critically ill newborns. Although the Epo group had half as many deaths as the placebo group, this finding did not reach statistical significance given the small number of participants. Reassuringly, the rate of moderate to severe neurodevelopmental impairment at 12 months was no higher in the Epo than in the placebo group, suggesting that any deaths that might have been prevented by Epo were unlikely to have led to a greater severity of neurodevelopmental abnormalities in surviving infants.

The relatively small size of this phase II trial is an important limitation. After post-hoc exclusion of 2 patients who later met exclusion criteria, the apparent benefit of Epo on 12-month outcomes was no longer statistically significant. Without a standardized approach to EEG data collection, we were limited in our ability to accurately diagnose clinical and electrographic seizures across all sites. Similarly, we were unable to compare MR spectroscopy and diffusion tensor imaging measures across centers due to lack of uniform data collection

procedures. Our findings require confirmation in a larger study with an adequate sample size to mitigate bias resulting from unavoidable chance confounding, with a longer period of follow-up to allow for the evaluation of long-term impacts, and with standardized neuroimaging and electrophysiological data collection across sites.

CONCLUSIONS

Among infants undergoing therapeutic hypothermia for HIE, multiple doses of Epo (1000 U/kg) given intravenously over 7 days may result in less MRI brain injury and may lead to improved short-term motor outcomes. Plans are underway to perform a large phase III trial to determine whether Epo treatment in conjunction with hypothermia improves the long-term neurologic outcome of infants with HIE.

ACKNOWLEDGMENTS

The following collaborators, in addition to those listed as authors, also participated in this study: Arkansas Children's Hospital: Andrea Ross, RN, Holly Pettit, RN, Nupur Dutta Chowdhury, MA, CCRP, and Billy Furgerson, PharmD; Children's National Health System: Avital Cnaan, PhD, Adrienne Arrieta, MS, James He, MS, and Kari Harris, MPH; Kaiser Permanente Santa Clara: Andrea Wickremasinghe; Stanford University: Anne DeBattista, PhD, C-PNP, C-PMHS, M. Bethany Ball, BS, CCRC, and Melinda Proud,

RCP; University of California, San Francisco: Donna Ferriero, MD, Colin Partridge, MD, Rebecca Webb, BS, and the University of California, San Francisco investigational drug service; University of Washington: Amy E. Silvia, ScM, Elizabeth L. Howland, Kathleen Washington, PhD, PT, and Niranjana Natarajan, MD; Washington University, St Louis: Anthony Barton.

Study data were collected and managed by using REDCap electronic data capture tools hosted at University of California, San Francisco.

We thank the DSMB members Robin Ohls, MD (Chair), John Barks, MD, and Janet Soul, MD, and the Independent Medical Monitor, Maureen Gilmore, MD, for their work. We thank Jessica Kan Vedder, BA MPH, for her organizational support of the study, for creating the study database, and for her detailed work in monitoring enrollment and data collection procedures. We also thank all the patients, families, and bedside nurses who participated in this study.

ABBREVIATIONS

AIMS: Alberta Infant Motor Scale
DSMB: data and safety monitoring board
Epo: erythropoietin
HIE: hypoxic-ischemic encephalopathy
IQR: interquartile range
WIDEA: Warner Initial Developmental Evaluation

This trial has been registered at www.clinicaltrials.gov (identifier NCT 01913340).

DOI: 10.1542/peds.2016-0191

Accepted for publication Mar 1, 2016

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PEDIATRICS (ISSN Numbers: Print, 0031-4005; Online, 1098-4275).

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FINANCIAL DISCLOSURE: The authors have indicated they have no financial relationships relevant to this article to disclose.

FUNDING: This study was funded by the Thrasher Research Fund.

POTENTIAL CONFLICT OF INTEREST: The authors have indicated they have no potential conflicts of interest to disclose.

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Pediatrics; originally published online May 2, 2016;

DOI: 10.1542/peds.2016-0191

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The online version of this article, along with updated information and services, is located on the World Wide Web at:

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