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High Dose Erythropoietin in ELGANs does not Alter Risk of Retinopathy of Prematurity

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Abstract

Introduction: The Preterm Erythropoietin (Epo) Neuroprotection (PENUT) Trial sought to determine the safety and efficacy of early high-dose Epo as a potential neuroprotective treatment. We hypothesized that Epo would not increase the incidence or severity of retinopathy of prematurity (ROP).

Methods: 941 infants born between 24-0/7 to 27-6/7 weeks' gestation were randomized to 1000 U/kg Epo or placebo intravenously for 6 doses, followed by subcutaneous or sham injections of 400 U/kg Epo three times a week through 32 weeks post menstrual age. In this secondary analysis of PENUT Trial data, survivors were evaluated for ROP. A modified intention-to-treat approach was used to compare treatment groups. In addition, risk factors for ROP were evaluated using regression methods that account for multiples, and allow adjustment for treatment and gestational age at birth.

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Statement of Ethics: This study was approved by the University of Washington Human Subjects Division and all site IRBs. This study was registered with the FDA (IND#12656) and [ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT01378273) (NCT01378273).

Data Sharing Statement: De-identified individual participant data will be made available through the NINDS Data Archive: <https://www.ninds.nih.gov/Current-Research/Research-Funded-NINDS/Clinical-Research/Archived-Clinical-Research-Datasets>. The data will be de-identified and a limited access data set will be available after September 2020 through a request form on that page. Data dictionaries, in addition to study protocol, the statistical analysis plan, and the informed consent form will be included. The data will be made available upon publication of all PENUT Trial related manuscripts to researchers who provide a methodologically sound proposal for use in achieving the goals of the approved proposal.

Results: Of 845 subjects who underwent ROP examination, 503 were diagnosed with ROP with similar incidence and severity between treatment groups. Gestational age at birth, birth weight, prenatal magnesium sulfate, maternal antibiotic exposure, and presence of heart murmur at 2 weeks predicted development of any ROP, while being on high frequency oscillator or jet ventilation (HFOV/HFJV) at 2 weeks predicted severe ROP.

Conclusion: Early high dose Epo followed by maintenance dosing through 32 weeks does not increase the risk of any or severe ROP in ELGANs. Gestational age, birth weight, maternal treatment with magnesium sulfate, antibiotic use during pregnancy, and presence of a heart murmur at 2 weeks were associated with increased risk of any ROP. Treatment with HFOV/HFJV was associated with an increased risk of severe ROP.

[ClinicalTrials.gov \(NCT01378273\)](https://clinicaltrials.gov/ct2/show/study/NCT01378273).

Keywords

retinopathy of prematurity; erythropoietin; extreme prematurity

Introduction:

Retinopathy of prematurity (ROP) remains one of the major morbidities of infants born at extremely low gestational age (ELGANs). In a study of 9575 extremely preterm infants, Stoll, et al., found the incidence and severity of ROP to be inversely related to gestational age at birth: 89% of infants born at 24 weeks gestation, 79% of infants born at 25 weeks gestation, 65% of infants born at 26 weeks gestation and 49% of those born at 27 weeks gestation develop some stage of ROP [1]. Severe ROP (stage 3) decreased from 42% at 24 weeks to 7% at 27 weeks gestation. Intervention for severe ROP decreased from 35% at 24 weeks gestation to 4% at 27 weeks gestation [1].

Early studies of erythropoietin (Epo) treatment to minimize transfusions and lower donor exposure in preterm infants suggested it was possible to achieve these goals [2,3]. However, these studies provided limited evidence for both safety and efficacy as most included a small number of patients, were retrospective analyses, or lacked contemporary control groups. In 2006, a Cochrane review suggesting an increased incidence and severity of ROP after early Epo use significantly decreased the clinical the use of Epo [4]. More recent meta-analyses based on additional prospective randomized controlled studies did not support this concern [5–7].

There has been increasing interest in using Epo as a neuroprotective therapy, as preclinical and phase I/II studies of this treatment have been promising [8–12]. As little Epo crosses the blood brain barrier [13], higher doses of Epo have been recommended for neuroprotection [14]. The safety of these higher dose regimens must be further investigated, with a specific focus on ROP as this has previously been called out as an area of concern. In the present study, we compare the rates of ROP among infants treated and not treated with Epo and investigate the prognostic value of early predictors of ROP.

Materials and Methods:

The Preterm Epo Neuroprotection (PENUT) Trial is a phase III randomized placebo-controlled double-blinded trial in which 941 infants born between 24 0/7 weeks and 27 6/7 weeks' gestation were randomized to neuroprotective doses of Epo from the first day after birth to 32 weeks post-menstrual age (PMA) [15]. Infants were enrolled at 19 sites across the United States between December 2013 and September 2016 [16]. Subjects received 1000 U/kg Epo or placebo intravenously for 6 doses, followed by subcutaneous injections of 400 U/kg Epo or sham injections three times a week through 32 weeks PMA.

This study was approved by the University of Washington Human Subjects Division and all site IRBs. This study was registered with the FDA (IND#12656) and [ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT01378273) (NCT01378273). Parents provided written informed consent.

ROP Evaluation

In this secondary analysis, surviving infants were evaluated for ROP following the 2013 American Academy of Pediatrics guidelines [16]. Examinations for ROP were completed at each site by qualified ophthalmologists and classified following the International Classification of Retinopathy of Prematurity guidelines (stage, zone, pre-plus disease) [17]. Any ROP was defined by evidence of retinal abnormalities compatible with ROP of any stage. ROP determined to require intervention (severe ROP) as recommended by the American Academy of Pediatrics guidelines was treated with laser photocoagulation, cryotherapy or bevacizumab [16].

Candidate Predictors

Sixty demographic and clinical variables obtained prior to the ROP exam were deemed clinically and statistically appropriate to be investigated as predictors of ROP. These variables were chosen based on statistical association with ROP found in this study. We examined the following parental characteristics (n=3 variables): race, ethnicity, and maternal education. Maternal health variables (n=12) were also assessed such as prenatal care, prolonged rupture of membranes, chorioamnionitis, maternal hypertension (pregnancy-induced hypertension, pre-eclampsia, or eclampsia), obesity, preterm labor, antenatal steroids, antibiotic exposure, antenatal magnesium sulfate, multiple gestation, mode of delivery and whether drugs, alcohol, or prescription drugs were used during pregnancy. Neonatal characteristics (n=7) examined included gestational age (24, 25, 26, 27 weeks), birth weight, small for gestational age status, occipital frontal circumference <10th percentile, Apgar scores <5 at 5 minutes, whether delayed cord clamping was performed, and whether intubation or chest compressions were performed during resuscitation after birth. We also examined post-birth events and exposures (n=5) from day 0 thru 28 including exam findings, ventilatory support at 28 days of life, presence of a heart murmur, the number and cumulative volume of packed red blood cell (PRBC) transfusions, and iron dosing. Some variables that were collected were not included if very common among all subjects (prevalence >95% of subjects), very infrequent (prevalence <5% of subjects), or missing in more than 10% of subjects.

Statistical Analysis

The modified intention-to-treat population included all 936 randomized ELGANs who received the first study dose, of which 845 infants were evaluated for ROP. Risks of any and severe ROP among Epo and placebo groups were compared using generalized estimating equations (GEE) [18] with robust standard errors to account for twins/multiples, adjusting for gestational age at birth.

Extremely unbalanced binary predictors (<5% or >95% in one group), and those predictors with very high intercorrelations (multicollinearities) were removed (Table S1). Remaining predictors were first evaluated by adding each individually to a univariate GEE model, adjusting for treatment assignment and gestational age. All significant predictors ($p < 0.05$) with less than 10% missing values were subsequently added in separate multivariable GEE models predicting any ROP and severe ROP. Predictors that remained statistically significant ($p < 0.05$) were used to generate a prediction model, and prognostic performance was evaluated using area under the receiver operating characteristics curve for the final model. GEE models were not adjusted for multiple testing, and significance levels were set at 0.05 for both univariate and multivariable models.

All statistical analyses were conducted using R statistical software package, Version 3.6.0 (Vienna, Austria).

Results:

The CONSORT diagram is shown in Figure S1. Of the 476 infants assigned to Epo, 9.9% died prior to having a ROP exam, and 1% were alive but not examined for a total of 424 infants or 89.1% included in this analysis; of the 460 infants assigned to placebo, 7.8% died prior to exam, 0.7% were alive but not examined, for a total of 421 or 91.5% included in this analysis.

Of 845 ELGANs who underwent ROP examination, 503 were diagnosed with ROP (stage 1–5) (Figure 1). Epo treatment did not significantly alter the stage of ROP compared with placebo. Stage 3 or 4 ROP was diagnosed in 16.6% of placebo-treated infants, and 14.1% of Epo-treated infants ($p = 0.79$), with severe ROP (treated) observed in 33 infants (8%) in the placebo group and 39 (9%) infants in the Epo group ($p = 0.40$). The median corrected gestational age at which intervention for severe ROP occurred in the control group was 36 weeks 4 days (IQR: 35 weeks 5 days, 38 weeks 2 days) compared to 36 weeks 1 day (IQR: 35 weeks 0 day, 38 weeks 1 day) in the Epo group ($p = 0.44$, Wilcoxon rank sum test). When divided into the stratification groups, infants born at 24–25 weeks underwent ROP interventions at a median of 36 weeks 1 day (IQR: 35 weeks 0 days, 37 weeks 3 days) versus 37 weeks 6 days (IQR: 36 weeks 0 days, 40 weeks 6 days) for infants born at 26–27 weeks ($p = 0.012$, Wilcoxon rank sum test). Treatment allocation again did not differ between groups.

The Epo group and the control group had identical rates of 9.8% pre-plus disease overall. This finding decreased from 18% in subjects born at 24 weeks gestational to 4% at 27 weeks

gestation. No statistical differences were noted for pre-plus disease between treatment allocation groups at any gestational age.

Table 1 compares the parental demographics and prenatal characteristics of all evaluated infants separated by ROP status. In single variable analysis, infants born to non-black parents, and those with mothers without preterm labor, treated with antibiotics, or treated with magnesium sulfate were more likely to develop ROP. Table 2 shows infant birth characteristics separated by ROP status. Infants who developed any ROP were less mature and more likely to be intubated at birth, from multiple gestation pregnancies, had lower 1-minute APGAR scores, and had lower weights, lengths, and head circumferences at birth. When clinical course was compared between those who developed ROP and those who did not (Table 3), oxygen requirement at 28 days was associated with significantly higher risk of any ROP. A higher number and greater cumulative volumes of PRBC transfusion, as well as treatment with high frequency oscillator or high frequency jet ventilation (HFOV/HFJV) at 14 days, were associated with significantly higher risks of any and severe ROP. While higher cumulative enteral iron intake up to 28 days is associated with lower risk of any and severe ROP, those associations were no longer present in multivariable analysis.

The incidence and severity of ROP was inversely related to gestational age at birth, and the distribution of severity was not affected by treatment group (Table 2 and Figure S2). In a multivariable model, gestational age at birth, infant weight at birth ($p<0.001$), prenatal magnesium sulfate ($p=0.01$), presence of heart murmur at 2 weeks of age, and antibiotic use during pregnancy ($p=0.02$) predicted development of any ROP (Figure 2), while being on HFOV/HFJV at 2 weeks ($p=0.01$) (Figure S3) predicted severe ROP.

In this study population, the area under the receiver operating curve based solely on gestational age and weight at birth is 0.756 (95% CI of 0.723–0.789). Including the three additional variables that were significantly associated with the development of any ROP in multivariable models did not significantly improve the area under the curve (AUC: 0.769; 95% CI: 0.737–0.801).

Discussion:

Previous studies have raised the concern that Epo might increase the risk of ROP in preterm infants. Most studies were small, single center, retrospective, or were not controlled. Furthermore, a wide range of Epo dose and duration were used, so they lacked the power to demonstrate safety. In a series of Cochrane Reviews, the available literature was analyzed to evaluate this concern. In the first Cochrane Review, Aher and Ohlsson [19] performed a meta-analysis on 2 studies [20,21] that examined the use of early versus late Epo for prevention of RBC transfusion and donor exposure. Some of the included data was obtained from the authors and was not previously published. They reported an increased risk of any ROP in infants treated with Epo compared to control, and a trend for ROP stage 3 with early Epo treatment. The authors recommended against both early and late Epo administration for treatment for anemia in preterm infants due to perceived lack of benefit (the number of donor exposures was not decreased) and concern for higher ROP risk.

Aher and Ohlsson published updated Cochrane Reviews in 2014 [5, 6], 2017 [7] and 2020 [8]. As more published studies were included, the results suggested that Epo was not associated with an increased risk of ROP. However, because of the limited clinical value of decreased transfusion number and donor exposure, they still did not recommend routine use of Epo in low birth weight or preterm infants despite finding that Epo significantly reduced the risk of intraventricular hemorrhage, periventricular leukomalacia and necrotizing enterocolitis.

The PENUT Trial is the largest clinical trial enrolling ELGANs, using high dose Epo for the longest duration [15]. Using this study protocol, we found no evidence that early high dose Epo followed by maintenance Epo increased the risk of any ROP, or severe ROP. Predictors of ROP included antibiotic use during pregnancy and labor, maternal treatment with magnesium sulfate, gestational age at birth, birth weight, and infant heart murmur at 2 weeks of age. Magnesium sulfate prophylaxis for fetal neuroprotection is commonly used in mothers threatening to deliver prematurely [22, 23]. The American College of Obstetrics and Gynecology has published two Committee Opinions recommending its use, but has not raised concerns regarding elevated ROP risk. [24, 25]. Further study of this association is warranted.

Several other factors, previously associated with the risk of development of ROP [26,27] did not reach statistical significance (black maternal race and any ROP ($p=0.053$): transfusion volume ($p=0.057$) and black paternal race ($p=0.054$) and severe ROP) in this study. Lust,et al., found a significant association between transfusion within the first 10 days of life and the occurrence of severe ROP [28]. Black race has been protective against ROP [28].

Development of a predictive model based on data from this study did not enhance our ability to identify infants who should undergo ROP evaluations beyond use of gestational age and weight at birth alone. Other investigators have tried to develop predictive models for ROP to improve identification of infants at risk [28,29]. Ying, et al., performed a secondary analysis of the retrospective G-ROP study in 7483 infants who underwent ROP examinations [29]. For any ROP, the area under the ROC curves was 0.87 for any ROP and 0.89 for severe ROP. Owen, et al., identified 57 factors associated with ROP, but after step-wise regression analysis, remaining factors associated with ROP risk were gestational age at birth, birth weight, need for surgery and maternal magnesium prophylaxis [27]. The area under the ROC for these factors was 0.8641 compared to a value of 0.8489 using the traditional model of gestational age and birth weight. Both investigations used subject populations that differed from the current study. Additionally, while both of these investigations found higher AUC values than the current study, a substantial percentage of infants at risk for developing ROP (~11–15%) would be missed if these predictive models were utilized for screening purposes.

The limitations of these study include that it is a secondary analysis of PENUT Trial data, and no adjustments for multiple testing has been undertaken. However, all data used in this analysis was prospectively collected. Therefore the results should be considered exploratory and interpreted with caution.

Conclusions:

High dose Epo followed by maintenance Epo given to ELGANs did not alter the incidence nor the severity of ROP in infants 24 0/7 to 27 6/7 weeks gestation at birth. Gestational age at birth, birth weight, prenatal magnesium sulfate, presence of heart murmur at 2 weeks, and antibiotic use during pregnancy predicted development of any ROP, while being on HFOV/HFJV during first 2 weeks predicted severe ROP.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.

ROP Status by Treatment Group. In the Placebo group, 61.3% were diagnosed with ROP and 57.5% were diagnosed with ROP in the Epo group. No significant differences were noted between the study groups.

Figure 2.
Forest Plot of Predictors of Any ROP Disease. Significant differences were noted for decreasing gestational age birth, increasing birth weight, prenatal magnesium sulfate treatment, heart murmur at 2 weeks of age, and antibiotics during pregnancy.

Table 1.

Parental Demographics and Prenatal Characteristics by ROP Status

N=845 unless otherwise noted	No ROP (n=342)	Any ROP (n=426)	Severe ROP (n=77)	P_{any}, P_{severe}
Maternal age, mean (SD)	28.9 (6.3)	28.9 (6.2)	28.7 (5.7)	0.41, 0.86
Maternal ethnicity, n (row %)				0.26, 0.07
Hispanic/Latino (n=179)	65 (36%)	95 (53%)	19 (11%)	
Not Hispanic/Latino (n=655)	272 (42%)	328 (50%)	55 (8%)	
Unknown/Not Reported (n=11)	5 (46%)	3 (27%)	3 (27%)	
Maternal race, n (row %)				<0.001, <0.001
Black or African American (n=218)	103 (47%)	106 (49%)	9 (4%)	
White (n=549)	209 (38%)	282 (51%)	58 (11%)	
All Others (n=78)	30 (38%)	38 (49%)	10 (13%)	
Preterm labor, n (row %)				0.01, 0.01
Yes (n=536)	224 (42%)	270 (50%)	42 (8%)	
No (n=309)	118 (38%)	156 (50%)	35 (11%)	
Antibiotics during pregnancy, n (row %)				0.03, 0.72
Yes (n=311)	103 (33%)	176 (57%)	32 (10%)	
No (n=534)	239 (45%)	250 (47%)	45 (8%)	
Prenatal magnesium sulfate treatment, n (row %)				0.003, 0.048
Yes (n=680)	260 (38%)	352 (52%)	68 (10%)	
No (n=165)	82 (50%)	74 (45%)	9 (5%)	
Paternal ethnicity, n (row %)				0.26, 0.70
Hispanic/Latino (n=172)	64 (37%)	90 (52%)	18 (11%)	
Not Hispanic/Latino (n=605)	246 (41%)	307 (51%)	52 (8%)	
Unknown/Not Reported (n=68)	32 (47%)	29 (43%)	7 (10%)	
Paternal race, n (row %)				0.71, 0.01
Black or African American (n=223)	100 (45%)	115 (52%)	8 (3%)	
White (n=491)	190 (39%)	249 (51%)	52 (10%)	
All Others (n=131)	52 (40%)	62 (47%)	17 (13%)	

P_{any} is a Wald test p -value of the individual covariate of interest in a GEE model predicting any ROP (vs. no ROP), adjusted for gestational age in weeks and randomized treatment assignment. Similarly, P_{severe} denotes the Wald test p -value predicting severe ROP (vs. no ROP).

Table 2.

Infant Birth Characteristics Separated by ROP Status

N=845 unless otherwise noted	No ROP (n=342)	ROP (n=426)	Severe ROP (n=77)	<i>P</i> any, <i>P</i> severe
Multiple gestation, n (row %)				0.046, 0.49
Yes (n=219)	78 (36%)	119 (54%)	22 (10%)	
No (n=626)	264 (42%)	307 (49%)	55 (9%)	
Gestational age at birth, n (row %)				<0.001, <0.001
24 weeks (n=197)	24 (12%)	134 (68%)	39 (20%)	
25 weeks (n=217)	72 (33%)	123 (57%)	22 (10%)	
26 weeks (n=207)	100 (48%)	98 (47%)	9 (4%)	
27 weeks (n=224)	146 (65%)	71 (32%)	7 (3%)	
Gender, n (row %)				0.38, 0.33
Female (n=407)	163 (40%)	211 (52%)	33 (8%)	
Male (n=438)	179 (41%)	215 (49%)	44 (10%)	
Delivery method, n (row %)				0.15, 0.16
Vaginal (n=263)	115 (44%)	123 (47%)	25 (9%)	
Elective C-section (n=74)	32 (43%)	40 (54%)	2 (3%)	
Emergency C-section (n=508)	195 (38%)	263 (52%)	50 (10%)	
Physical Exam at Birth				
Weight, mean in grams (SD)				
Birth	893 (184)	768 (167)	674 (142)	<0.001, <0.001
14 Days (N=844)	944 (180)	822 (169)	726 (137)	<0.001, <0.001
Head circumference, mean in cm (SD)				
Birth (N=837)	23.9 (1.9)	22.8 (1.7)	22.0 (1.7)	0.003, 0.02
14 Days (N=803)	23.9 (1.5)	22.8 (1.7)	21.9 (1.4)	0.003, 0.001
Height, mean in cm (SD)				
Birth (N=804)	34.1 (2.8)	32.6 (2.7)	31.0 (2.4)	0.005, <0.001
14 Days (N=794)	35.0 (2.7)	33.3 (2.6)	32.2 (2.4)	0.001, 0.004
Intubation at Birth, n (row %)				0.03, 0.62
Yes (N=677)	244 (36%)	364 (54%)	69 (10%)	
No (N=168)	98 (58%)	62 (37%)	8 (5%)	
1-minute APGAR Score, mean (SD)	4.37 (2.32)	3.74 (2.18)	3.26 (2.09)	0.02, 0.09

*P*_{any} is a Wald test *p*-value of the individual covariate of interest in a GEE model predicting any ROP (vs. no ROP), adjusted for gestational age in weeks and randomized treatment assignment. Similarly, *P*_{severe} denotes the Wald test *p*-value predicting severe ROP (vs. no/mild ROP).

Table 3:

Clinical Course Variables Separated by ROP Status

N=845 unless otherwise noted	No ROP	ROP (n=426)	Severe ROP (n=77)	<i>P</i> any, <i>P</i> severe
Oxygen requirement at 28 days, n (%)				<0.001, 0.29
Yes (n=750)	281 (37%)	396 (53%)	73 (20%)	
No (n=95)	61 (64%)	30 (32%)	4 (4%)	
Heart murmur at 2 weeks of age, n (%)				0.049, 0.57
Yes (n=272)	93 (34%)	151 (56%)	28 (10%)	
No (n=573)	249 (43%)	275 (48%)	49 (9%)	
Treatments				
Randomized treatment, n (%)				0.79, 0.33
Epo (n=424)	179 (42%)	206 (49%)	39 (9%)	
Placebo (n=421)	163 (39%)	225 (53%)	33 (8%)	
PRBC transfusion volume, first 14 days				
Median count (IQR)	1 (0, 2)	2 (1, 4)	3 (2, 4)	0.02, <0.001
Median volume, mL (IQR)	12 (0, 27)	23 (11, 37)	36 (24, 48)	0.001, <0.001
HFOV/HFJV at 14 days, n (%)				<0.001, <0.001
Yes (N=241)	53 (22%)	140 (58%)	48 (20%)	
No (N=604)	289 (48%)	286 (47%)	29 (5%)	

*P*any is a Wald test *p*-value of the individual covariate of interest in a GEE model predicting any ROP (vs. no ROP), adjusted for gestational age in weeks and randomized treatment assignment. Similarly, *P*severe denotes the Wald test *p*-value predicting severe ROP (vs. no/mild ROP).