Effect of Early Prophylactic High-Dose Recombinant Human Erythropoietin in Very Preterm Infants on Neurodevelopmental Outcome at 2 Years: A Randomized Clinical Trial

Natalucci, Giancarlo; Latal, Beatrice; Koller, Brigitte; Rüegger, Christoph; Sick, Beate; Held, Leonhard; Bucher, Hans Ulrich; Fauchère, Jean-Claude

Abstract: IMPORTANCE Very preterm infants are at risk of developing encephalopathy of prematurity and long-term neurodevelopmental delay. Erythropoietin treatment is neuroprotective in animal experimental and human clinical studies. OBJECTIVE To determine whether prophylactic early high-dose recombinant human erythropoietin (rhEPO) in preterm infants improves neurodevelopmental outcome at 2 years’ corrected age. DESIGN, SETTING, AND PARTICIPANTS Preterm infants born between 26 weeks 0 days’ and 31 weeks 6 days’ gestation were enrolled in a randomized, double-blind, placebo-controlled, multicenter trial in Switzerland between 2005 and 2012. Neurodevelopmental assessments at age 2 years were completed in 2014. INTERVENTIONS Participants were randomly assigned to receive either rhEPO (3000 IU/kg) or placebo (isotonic saline, 0.9%) intravenously within 3 hours, at 12 to 18 hours, and at 36 to 42 hours after birth. MAIN OUTCOMES AND MEASURES Primary outcome was cognitive development assessed with the Mental Development Index (MDI; norm, 100 [SD, 15]; higher values indicate better function) of the Bayley Scales of Infant Development, second edition (BSID-II) at 2 years corrected age. The minimal clinically important difference between groups was 5 points (0.3 SD). Secondary outcomes were motor development (assessed with the Psychomotor Development Index), cerebral palsy, hearing or visual impairment, and anthropometric growth parameters. RESULTS Among 448 preterm infants randomized (mean gestational age, 29.0 [range, 26.0-30.9] weeks; 264 [59%] female; mean birth weight, 1210 [range, 490-2290] g), 228 were randomized to rhEPO and 220 to placebo. Neurodevelopmental outcome data were available for 365 (81%) at a mean age of 23.6 months. In an intention-to-treat analysis, mean MDI was not statistically significantly different between the rhEPO group (93.5 [SD, 16.0] [95% CI, 91.2 to 95.8]) and the placebo group (94.5 [SD, 17.8] [95% CI, 90.8 to 98.5]) (difference, -1.0 [95% CI, -4.5 to 2.5]; P = .56). No differences were found between groups in the secondary outcomes. CONCLUSIONS AND RELEVANCE Among very preterm infants who received prophylactic early high-dose rhEPO for neuroprotection, compared with infants who received placebo, there were no statistically significant differences in neurodevelopmental outcomes at 2 years. Follow-up for cognitive and physical problems that may not become evident until later in life is required. TRIAL REGISTRATION clinicaltrials.gov Identifier: NCT00413946.

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**TRIAL REGISTRATION**  clinicaltrials.gov Identifier: NCT00413946


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Although outcome in very preterm infants has improved in recent decades, they still experience significant long-term neurodevelopmental delay. The underlying pathology is termed encephalopathy of prematurity, as visualized by magnetic resonance imaging (MRI). Among several pharmacological candidates to prevent brain injury or improve development, erythropoietin (EPO) has been shown to be among the most promising. EPO stimulates erythroid cell proliferation, survival, and differentiation. More recent evidence suggests a role of EPO in tissue development and protection, and EPO receptor expression has been observed in other cell types such as endothelial, glial, and neuronal cells. Animal experiments first demonstrated neuroprotective activity of EPO. Potential mechanisms explaining this action include inhibition of glutamate release, modulation of intracellular calcium metabolism, generation of antiapoptotic factors, and anti-inflammatory and antioxidant effects. These preclinical data found support in the results of clinical trials assessing the neuroprotective role of recombinant human EPO (rhEPO) in term-born infants with hypoxic ischemic encephalopathy and stroke. Retrospective studies using rhEPO for anemia and a recent trial showed that EPO also improves neurodevelopmental outcome in preterm infants. These studies, however, were relatively small. To cross the blood-brain barrier, EPO has to be administered in high doses of 2000 to 5000 IU/kg of body weight. These high doses are well tolerated in preterm infants. A short treatment period sufficient to block brain receptors did not increase the risk for retinopathy of prematurity, in contrast to what has been reported after treatment over several weeks. An association has been reported between early high-dose rhEPO and a reduced incidence of white and gray matter injuries assessed by cerebral MRI in a subgroup of very preterm infants at term equivalent from this trial. This article reports the prespecified primary outcome, the effect of early high-dose rhEPO on neurodevelopmental outcome at 2 years.

Methods

Study Design
This phase 3 study was designed as a randomized, double-blind, placebo-controlled, multicenter trial with 1:1 allocation of patients to high-dose rhEPO or placebo. Five Swiss perinatal centers, 3 university hospitals (Basel, Geneva, and Zurich) and 2 district hospitals (Aarau and Chur), were included in the study. Enrollment occurred between 2005 and 2012, with the date of last neurodevelopmental evaluation in 2014. Vials containing the study drug were prepared in the pharmacy of Zurich University Hospital according to a randomization list stratified per center and labeled, shipped, and stored according to the Swiss Therapeutic Products Act. The randomization list was known only to the pharmacist. Parents, physicians, nurses, and external statisticians were unaware of treatment allocation. All neurodevelopmental assessments were conducted in a blinded manner. Approval to conduct this study was granted by the ethical committee of the Zurich University Children's Hospital, the ethical committee of Canton Zurich, and the Swiss Agency for Therapeutic Products (Swissmedic). Written informed consent was obtained from the parents of eligible infants.

Study Population
The study protocol (Supplement 1) has been described previously. Briefly, very preterm infants born between 26 weeks 0 days and 31 weeks 6 days' gestation were eligible for enrollment within the first 3 hours after birth. Exclusion criteria were a genetically defined syndrome, a severe congenital malformation adversely affecting life expectancy or neurodevelopment, severe intraventricular hemorrhage before randomization, and a priori palliative care.

Intervention
rhEPO or an equivalent volume of isotonic saline (NaCl, 0.9%) placebo was administered intravenously before 3 hours, at 12 to 18 hours, and at 36 to 42 hours after birth. A single dose consisted of 25μg (3000 IU) rhEPO per kg of body weight dissolved in 1mL distilled water. One mL per kg birth weight was administered intravenously during a period of 3 minutes. The maximal dose was 1.5 mL (37.5μg [4500 IU]) rhEPO for infants weighing 1.5 kg or more. Similarly, the placebo dose consisted of 1 mL of NaCl (0.9%) per kilogram birth weight.

Monitoring
Serial cerebral ultrasound assessment was carried out on day 1, days 7 to 10, and then every 14 days until 36 weeks 0 days' postmenstrual age or at discharge if discharged before study. Drug and all other medications were documented, as well as any complications.

The Swissmedic temporally suspended the study after an infant in the study died of severe intracranial hemorrhage and the parents lodged a claim for compensation. The parents considered this critical event to be attributable to the experimental drug; disclosure of group allocation revealed that the infant was in the rhEPO group. The ethics committees and Swissmedic asked for a review by independent experts, who concluded that there was no evidence for a causal relation between rhEPO and intracranial hemorrhage. Neither the investigators nor the statisticians were involved in the review by the independent experts and remained blinded to the outcomes. After an 11-month hold, enrollment continued with the following constraint: Infants with hemorrhage grade 2 or more detected before dose 3 of rhEPO had to be excluded.

Definition of Neonatal and Demographic Variables
Gestational age was defined as the best estimate available from obstetric measurements based on the last menstrual period or prenatal ultrasound findings, as recorded in the maternal chart. Z scores for anthropometric measures were calculated based on the growth curves by Voigt et al. Major brain injury was defined by cerebral ultrasound examination as severe intraventricular hemorrhage, ie, grade 2 or more according to Volpe, cystic periventricular leukomalacia, or both. Bronchopulmonary dysplasia was defined as requirement for additional oxygen at 36 weeks 0 days' postmenstrual age. Retinopathy of prematurity was defined using the International Committee criteria. Necrotizing enterocolitis was defined as pneumatosis intestinalis or portal venous gas (Bell stage ≥2). Infection was classified as uninfected or proven sepsis (positive blood or cerebrospinal fluid culture). Socioeconomic status was estimated by a validated
Early Prophylactic High-Dose rhEPO for Very Preterm Infants

Original Investigation Research

We added 20%, targeting at least 211 infants per group. χ² test were used to compare baseline characteristics between groups.

Outcome Assessment

Neurodevelopmental examination was performed at 2 years' corrected age by experienced developmental pediatricians or neuropediatricians at 5 follow-up sites attached to the perinatal centers participating in the study. Examinations were videotaped and regular meetings of the investigators were scheduled. The assessment consisted of a clinical examination including anthropometric measurement, a structured neurologic assessment, and a developmental assessment using the Bayley Scales of Infant Development, second edition (BSID-II).26 Infants who were so severely impaired that structured testing with the BSID-II could not be performed were assigned a mental development index (MDI) and psychomotor development index (PDI) of 49 (±3 SD). Norm value of both MDI and PDI is 100 (SD, 15), with high values indicating better function. Cerebral palsy was graded according to the Gross Motor Function Classification System of Palisano et al27 for children 2 years or younger. Vision and hearing were assessed either by direct examination or parents' report. Severe hearing impairment was defined as the absence of useful hearing, even with aids (ie, >90 dB hearing level); severe visual impairment was defined as blindness or only perception of light or light-reflecting objects. The composite outcome category “severe neurodevelopmental impairment” was defined as 1 or more of the following: a BSID-II index less than 2 SDs below the mean (ie, MDI or PDI <70); cerebral palsy with Gross Motor Function Classification System level 3 to 5; severe hearing or visual impairment.

Results

Study Population

Of 1359 live-born infants within the target gestational age range, 450 were enrolled and randomized (Figure) (mean gestational age, 29.0 [range, 26.0-30.9] weeks; 264 [59%] female; mean birth weight, 1210 [range, 490-2290] g). Among them, 230 were allocated to receive rhEPO and 220 to receive placebo. After discharge from the neonatal intensive care unit, 2 randomized infants who had been allocated to the rhEPO group were diagnosed with a syndrome potentially affecting neurodevelopment. For this reason, they were retrospectively excluded from the outcome analysis. The number of randomized infants in 2 previous reports14,15 slightly differs from that in the present report because 12 infants initially included were later found not to meet inclusion criteria. Baseline characteristics were similar,12 except for a higher 5-minute Apgar score in the rhEPO vs placebo group (P = .02), as were neonatal morbidities (Table 1). The proportion of dropouts and infants assessed with developmental tests other than the BSID-II were also similar in both groups (Figure). Primary outcome data were collected at age 2 years from 191 infants in the rhEPO group (83%) and 174 in the placebo group (79%). Mean age at outcome assessment was 23.6 months and similar between groups.

Of 450 randomized infants, 7 (1.5%) received a lower dose of rhEPO or placebo than allocated and 50 (11%) received supplemental rhEPO to treat anemia of prematurity during the neonatal course. The distributions of these infants with lower dose (4 in the rhEPO group and 3 in the placebo group) and with supplement-
rhEPO indicates recombinant human erythropoietin.  
*Decision to provide primary nonintervention and palliative care after delivery was made antenatally with the agreement of the parents if several known prognostic factors were so unfavorable that the initiation of intensive care measures appeared to be inappropriate.

Infants received lower than allocated dose because after randomization, which occurred before 3 hours of life, exclusion criteria (n = 5) or nonadherence to inclusion criteria (attributable to errors in reporting of gestational age, n = 2) were discovered for some infants; thus, they were excluded after randomization.

Infants received supplemental rhEPO later to treat anemia of prematurity during the neonatal course.

*Excluded after administration of the allocated treatment because of a uniparental disomy 16 and a dysmorphic syndrome that became evident after the third day of life (genetic investigations were still ongoing at the time of manuscript submission).

Figure. Participant Flow in the Clinical Trial of Erythropoietin in Preterm Infants

1359 Infants born >26 wk to <32 wk gestation in 2005-2012

450 Randomized

199 Received rhEPO as randomized
31 Did not receive rhEPO as randomized
27 Received supplemental rhEPO

191 Included in primary analysis (underwent Bayley Scales of Infant Development II)
39 Excluded
31 Did not undergo follow-up assessment
8 Underwent other developmental test
4 Griffith Mental Development Scales
4 Bayley Scales of Infant and Toddler Development

199 Underwent follow-up assessment
29 Did not undergo follow-up assessment
16 Dropped out
13 Died

186 Underwent follow-up assessment
34 Did not undergo follow-up assessment
22 Dropped out
12 Died

174 Included in primary analysis (underwent Bayley Scales of Infant Development II)
46 Excluded
34 Did not undergo follow-up assessment
12 Underwent other developmental test
8 Griffith Mental Development Scales
4 Bayley Scales of Infant and Toddler Development

230 Randomized to receive rhEPO
194 Received placebo as randomized
26 Did not receive placebo as randomized
23 Received supplemental placebo

220 Randomized to receive placebo
194 Received placebo as randomized
26 Did not receive placebo as randomized
3 Received lower dose
23 Received supplemental placebo

2 Excluded (met exclusion criteria)

909 Excluded

621 Parents not approached (a priori palliative care included)
176 Parental refusal
86 Severe congenital malformation
26 Participation in another trial

Discussion
In this randomized, double-blind, placebo-controlled, multicenter trial enrolling very preterm infants treated with either early high-dose rhEPO or saline placebo after birth, no effect of rhEPO on neurodevelopmental outcomes at 2 years’ corrected age could be demonstrated. To the best of our knowledge, this study evaluated the largest population to date of very preterm infants treated with high-dose rhEPO during the first days of life. It is possible that rhEPO does not have a neuroprotective role. However, differences with previous studies suggest the results of this study may be related to the timing and duration of rhEPO administration. Two previous smaller randomized clinical trials and 2 retrospective studies demonstrated a beneficial effect of EPO. In contrast, another randomized clinical trial found no effect from repeated administration of low-dose rhEPO together with iron supplementation over 6 weeks on neurodevel-
velopmental outcome measurements in extremely low birth weight infants at 18 to 22 months’ corrected age. The fundamental differences between these studies and the present one are the sample sizes and the rhEPO treatment regimens. In the 2 smaller randomized trials, rhEPO was started later (between day 2 and 4 of life), given in lower doses (400 IU/kg), more often (3×/wk), and over a longer period (up to 35 weeks’ postmenstrual age) than in the present study. Therefore, one of the reasons for the lack of improved outcome with rhEPO in this study could be the timing of the first dose and shorter duration of rhEPO treatment.

In extremely low birth weight infants, high-dose rhEPO (2500 IU/kg) achieves neuroprotective plasma concentrations over 12 hours after injection, and in case of repeated administrations, steady-state conditions are achieved within 24 to 48 hours. We decided on a high-dose regimen over a short duration immediately after birth to rapidly saturate erythropoietin receptors while reducing any adverse effects of high-dose rhEPO treatment. However, in a retrospective analysis, Brown et al reported an association between greater 6-week cumulative doses of rhEPO and higher cognitive scores assessed by the BSID-II in very preterm infants at a median age of 26 months, suggesting a possible dose-response relationship between rhEPO and the outcome measure. The regimen used in this study might be insufficient in achieving neuroprotection during the postnatal period, and the standard application of rhEPO for neuroprotection in very preterm infants still needs to be clarified.

To date, 2 other large trials have been designed to analyze the neuroprotective role of rhEPO in very preterm infants: one is completed (NCT02036073), and the other is still ongoing (NCT01378273). According to their protocols, rhEPO is given in lower dose and more often (ie, 500 IU/kg every day for 14 days, beginning at <24 hours of age; and 1000 IU/kg intravenously every 48 hours for 6 doses, then 400 IU/kg subcutaneously 3 times per week until 32 weeks 6 days postmenstrual age) than in the present study. The results of these studies should help in assessment of the different rhEPO strategies.

In a retrospective cohort study of extremely preterm infants, Neubauer et al reported improvement in neurodevelopmental outcome in infants who were exposed to EPO and had neonatal brain lesions. This was not observed in this trial. However, lower gestational age groups, ie, less than 26 weeks, and infants with severe morbidities, such as major brain lesions that can affect neurodevelopment, were underrepresented in this study sample, which might have prevented identification of a neuroprotective role of rhEPO in high-risk preterm subpopulations. It is surprising that we found no treatment effect of rhEPO on the primary outcome, MDI, in the subgroup of study infants in which an association between rhEPO and reduced incidence of white and gray matter injuries at term equivalent was previously shown. However, correlation between quantitative measures using cerebral MRI at term-equivalent age and qualitative measures of cognitive outcome at 2 years in preterm infants has not been established, and the search for imaging biomarkers continues. The neurodevelopmental outcome at age 5 years in this cohort will be important. An ongoing trial (NCT02076373) is examining whether a selected group of very preterm infants with intraventricular hemorrhage grade 2 or more could benefit from high-dose rhEPO administered as a rescue therapy.

### Table 1. Comparison of Baseline Characteristics Between the Study Groups

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>rhEPO (n = 191)</th>
<th>Placebo (n = 174)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gestational age, mean (SD), wk</td>
<td>29.2 (1.6)</td>
<td>29.3 (1.6)</td>
</tr>
<tr>
<td>Girls, No. (%)</td>
<td>71 (37)</td>
<td>76 (44)</td>
</tr>
<tr>
<td>Singleton, No. (%)</td>
<td>120 (63)</td>
<td>114 (65)</td>
</tr>
<tr>
<td>Birth weight, mean (SD), g</td>
<td>1220 (327)</td>
<td>1213 (357)</td>
</tr>
<tr>
<td>z score, mean (SD)</td>
<td>−0.08 (0.76)</td>
<td>−0.13 (0.88)</td>
</tr>
<tr>
<td>Birth head circumference, mean (SD), cm</td>
<td>27.0 (2.0)</td>
<td>26.9 (2.3)</td>
</tr>
<tr>
<td>z score, mean (SD)</td>
<td>−0.10 (0.65)</td>
<td>−0.19 (0.75)</td>
</tr>
<tr>
<td>Antenatal steroids (complete course), No. (%)</td>
<td>186 (97)</td>
<td>158 (91)</td>
</tr>
<tr>
<td>Chorioamnionitis (placental histology), No. (%)</td>
<td>57 (30)</td>
<td>44 (25)</td>
</tr>
<tr>
<td>Umbilical artery pH, mean (SD)</td>
<td>7.32 (0.07)</td>
<td>7.32 (0.08)</td>
</tr>
<tr>
<td>Apgar score at 5 min, mean (SD)</td>
<td>7.8 (1.6)</td>
<td>7.3 (2.0)</td>
</tr>
<tr>
<td>Mechanical ventilation, median (IQR), d</td>
<td>0.0 (0.0 to 4.0)</td>
<td>0.0 (0.0 to 3.0)</td>
</tr>
<tr>
<td>Branchpulmonary dysplasia, No. (%)</td>
<td>66 (34)</td>
<td>64 (37)</td>
</tr>
<tr>
<td>IVH grade ≥2, No. (%)</td>
<td>10 (5)</td>
<td>10 (6)</td>
</tr>
<tr>
<td>Cystic periventricular leukomalacia, No. (%)</td>
<td>1 (0.5)</td>
<td>2 (1)</td>
</tr>
<tr>
<td>Sepsis, No. (%)</td>
<td>24 (13)</td>
<td>22 (13)</td>
</tr>
<tr>
<td>Necrotizing enterocolitis, No. (%)</td>
<td>4 (2)</td>
<td>5 (3)</td>
</tr>
<tr>
<td>ROP grade ≥3, No. (%)</td>
<td>1 (0.5)</td>
<td>5 (3)</td>
</tr>
<tr>
<td>PDA (treatment needed), No. (%)</td>
<td>55 (29)</td>
<td>44 (25)</td>
</tr>
<tr>
<td>Socioeconomic status, median (IQR)</td>
<td>6.0 (4.0-6.0)</td>
<td>6.0 (4.0-7.0)</td>
</tr>
<tr>
<td>Maternal age, median (IQR), y</td>
<td>33.5 (29.0-37.0)</td>
<td>33.0 (29.0-35.0)</td>
</tr>
<tr>
<td>Education of the mother, median (IQR)</td>
<td>3.0 (1.0-3.0)</td>
<td>3.0 (1.5-3.0)</td>
</tr>
</tbody>
</table>

Abbreviations: IQR, interquartile range; IVH, intraventricular hemorrhage; PDA, patent ductus arteriosus; rhEPO, recombinant human erythropoietin; ROP, retinopathy of prematurity.

* Two doses of 12 mg or 4 doses of 6 mg of betamethasone administered intramuscularly 24 hours apart.

** Twelve-point score classified into higher (score 2-5), middle (6-8), and lower (9-12) class.

Six-point score classified into higher (score 1-2), middle (3-4), and lower (5-6) education.

The negative results of the trial also raise a question about the timing of measurement of the primary outcome. As recently pointed out by Marlow, assessment of outcomes at 2 years may not be the most appropriate point to assess the efficacy of an intervention, and the time point may rather reflect proof of safety. The predictive validity of long-term neurodevelopmental outcome for individuals assessed at 2 years is relatively poor if infants with major disabilities are excluded. Thus, the present study assessing outcomes at 2 years’ corrected age may primarily confirm the previously reported safety of high-dose rhEPO administration to very preterm infants born between 26 and 32 weeks’ gestational age. Assessment at school age may be a better measure of efficacy, when children’s cognitive performance becomes more differentiated than at 2 years, and reevaluation of the cohort at this age is planned. To date there is not enough evidence to support the administration of rhEPO for neuroprotection in very preterm infants.
The strengths of this study include its randomized, double-blind, placebo-controlled design and the large sample size. However, some limitations also need to be mentioned. A first weakness is the administration of supplemental rhEPO to treat anemia in about one-tenth of the whole cohort, and the administration of a lower dose of rhEPO or placebo than allocated in 7 infants. Notwithstanding this protocol violation, similar results were observed in both the ITT and the per-protocol analyses, making the possibility of bias less relevant. A second limitation is the relatively long duration of enrollment, mainly caused by an 11-month enrollment stop by the Swissmedic and the ethics committees because of concern about the death of an infant allocated to the rhEPO group. A third limitation is that 5 follow-up centers were involved in outcome data collection, potentially increasing variability in the quantification of neurodevelopment. To reduce this potential source of bias, the follow-up examinations were performed by experienced investigators, videotaped, and discussed at regular meetings. Fourth, the 19% rate of loss to follow-up is of concern, although 6% represented deceased infants. Fifth, the placebo group had a considerably higher MDI than hypothesized in the planning phase of the study, which may have reduced the power of the study. This might have occurred because no preterm infants at very high risk for neurodevelopmental problems, ie, with gestational age less than 26 weeks or affected by high-grade intracerebral bleeding, were enrolled. In addition, improvement in neurodevelopmental outcomes of extremely preterm infants has been observed in Switzerland over the last decade.

**Conclusions**

Among very preterm infants who received prophylactic early high-dose rhEPO for neuroprotection, compared with infants who received placebo, there were no statistically significant differences in neurodevelopmental outcomes at 2 years. Follow-up for cognitive and physical problems that may not become evident until later in life is required.

**Table 2. Comparison of Neurodevelopmental Outcome Data Between the Study Groups (ITT)**

<table>
<thead>
<tr>
<th>Primary outcome</th>
<th>rhEPO (n = 191)</th>
<th>Placebo (n = 174)</th>
<th>Mean Difference (99% CI)*</th>
<th>Absolute Risk Reduction (99% CI)*</th>
<th>OR (99% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>MDI, mean (95% CI)</td>
<td>93.5 (91.2 to 95.8)</td>
<td>94.5 (90.8 to 98.5)</td>
<td>−1.0 (−4.5 to 2.5)</td>
<td>.56</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Secondary outcomes</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PDI, mean (95% CI)*</td>
<td>89.5 (86.2 to 92.6)</td>
<td>92.1 (88.9 to 96.0)</td>
<td>−2.6 (−7.7 to 1.7)</td>
<td>.15</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cerebral palsy, No. (%)</td>
<td>8 (4)</td>
<td>8 (5)</td>
<td>0.00 (−0.05 to 0.06)</td>
<td>1.0 (0.2 to 3.5)</td>
<td>&gt;.99</td>
<td></td>
</tr>
<tr>
<td>GMFCS 3, 4, and 5, No. (%)d</td>
<td>2 (1)</td>
<td>0</td>
<td>−0.01 (−0.04 to 0.02)</td>
<td>.98</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Severe hearing impairment, No. (%)</td>
<td>1 (0.5)</td>
<td>0</td>
<td>−0.00 (−0.04 to 0.03)</td>
<td>&gt;.99</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Severe visual impairment, No. (%)</td>
<td>2 (1)</td>
<td>0</td>
<td>−0.01 (−0.04 to 0.02)</td>
<td>.50</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Weight, mean (99% CI), g</td>
<td>11.7 (11.4 to 12.0)</td>
<td>11.8 (11.4 to 12.0)</td>
<td>−0.1 (−0.4 to 0.2)</td>
<td>.98</td>
<td></td>
<td></td>
</tr>
<tr>
<td>z score, mean (99% CI)</td>
<td>−0.15 (−0.35 to 0.05)</td>
<td>−0.08 (−0.36 to 0.08)</td>
<td>−0.01 (−0.3 to 0.1)</td>
<td>.83</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Length, mean (99% CI), cm</td>
<td>86.2 (85.2 to 87.1)</td>
<td>86.5 (85.7 to 87.3)</td>
<td>−0.3 (−1.3 to 0.6)</td>
<td>.47</td>
<td></td>
<td></td>
</tr>
<tr>
<td>z score, mean (99% CI)</td>
<td>−0.08 (−0.35 to 0.15)</td>
<td>−0.00 (−0.28 to 0.20)</td>
<td>−0.01 (−0.3 to 0.2)</td>
<td>.47</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Head circumference, mean (99% CI), cm</td>
<td>48.3 (48.0 to 48.6)</td>
<td>48.4 (48.0 to 48.7)</td>
<td>−0.01 (−0.5 to 0.2)</td>
<td>.91</td>
<td></td>
<td></td>
</tr>
<tr>
<td>z score, mean (99% CI)</td>
<td>−0.07 (−0.79 to −0.33)</td>
<td>−0.45 (−0.79 to −0.23)</td>
<td>−0.1 (−0.4 to 0.1)</td>
<td>.71</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Exploratory outcomes, No. (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Survival without severe NDI</td>
<td>164 (84)</td>
<td>148 (87)</td>
<td>0.02 (−0.09 to 0.13)</td>
<td>0.9 (0.4 to 1.9)</td>
<td>.76</td>
<td></td>
</tr>
<tr>
<td>MDI &lt;70e</td>
<td>12 (6)</td>
<td>15 (9)</td>
<td>0.02 (−0.04 to 0.09)</td>
<td>0.7 (0.2 to 2.0)</td>
<td>.43</td>
<td></td>
</tr>
<tr>
<td>PDI &lt;70e</td>
<td>21 (11)</td>
<td>17 (10)</td>
<td>−0.01 (−0.08 to 0.07)</td>
<td>1.2 (0.5 to 2.7)</td>
<td>.73</td>
<td></td>
</tr>
</tbody>
</table>

**Abbreviations:** GMFCS, Gross Motor Functions Classification System; ITT, intention to treat; MDI, Mental Development Index; NDI, neurodevelopmental impairment; OR, odds ratio; PDI, Psychomotor Development Index; rhEPO, recombinant human erythropoietin.

*d For primary outcome, 95% CI is reported.

**Reports as proportions of 1.

**A third limitation is that 5 follow-up centers were involved in outcome data collection, potentially increasing variability in the quantification of neurodevelopment. To reduce this potential source of bias, the follow-up examinations were performed by experienced investigators, videotaped, and discussed at regular meetings. Fourth, the 19% rate of loss to follow-up is of concern, although 6% represented deceased infants. Fifth, the placebo group had a considerably higher MDI than hypothesized in the planning phase of the study, which may have reduced the power of the study. This might have occurred because no preterm infants at very high risk for neurodevelopmental problems, ie, with gestational age less than 26 weeks or affected by high-grade intracerebral bleeding, were enrolled. In addition, improvement in neurodevelopmental outcomes of extremely preterm infants has been observed in Switzerland over the last decade.**

**Conclusions**

Among very preterm infants who received prophylactic early high-dose rhEPO for neuroprotection, compared with infants who received placebo, there were no statistically significant differences in neurodevelopmental outcomes at 2 years. Follow-up for cognitive and physical problems that may not become evident until later in life is required.
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