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Erythropoietin for the Repair of Cerebral Injury in Very Preterm Infants (EpoRepair)

A Randomized Controlled Trial: Background, Aims and Study Protocol

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Key Words
Brain damage · Children · Neurology · Development · Drug

Abstract
Background: Preterm infants suffering from intraventricular hemorrhage (IVH) are at increased risk for neurodevelopmental impairment. Observational data suggest that recombinant human erythropoietin (rEPO) improves long-term cognitive outcome in infants with IVH. Recent studies revealed a beneficial effect of early high-dose rEPO on white matter development in preterm infants determined by magnetic resonance imaging (MRI). ***Objectives:*** To summarize the current evidence and to delineate the study protocol of the EpoRepair trial (Erythropoietin for the Repair of Cerebral Injury in Very Preterm Infants). ***Methods:*** The study involves a review of the literature and the design of a double-blind, placebo-controlled, multicenter trial of repetitive high-dose rEPO administration, enrolling 120 very preterm infants with moderate-to-severe IVH diagnosed by cranial ultrasound in the first days of life, qualitative and quantitative MRI at term-equivalent age and long-term neurodevelopmental follow-up until 5 years of age. ***Results and Conclusions:*** The hypothesis generated by observational data that rEPO may improve long-term cognitive outcomes of preterm infants suffering from IVH are to be confirmed or refuted by the randomized controlled trial, EpoRepair.

Introduction

Despite a perpetual increase in survival rates of very preterm infants, the long-term neurodevelopmental outcome is still worrying. One of the most consistent predictors of neurodevelopmental impairment in preterm infants is intraventricular hemorrhage (IVH) [1–3], which is recognized in the first few days of life (DOL) by cranial ultrasound, the standard imaging tool for the diagnosis of cerebral lesions in preterm infants and graded according to the classification of Papile et al. [4].

The names and affiliations of the EpoRepair Investigators are listed in the Appendix.

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Infants with higher-grade IVH (grade III or IV, the latter of which is also termed 'hemorrhagic parenchymal infarction' [5]), especially those with posthemorrhagic hydrocephalus, are the most severely affected [6]. The impact of lower-grade IVH (grade I and II) on the neurodevelopment of preterm infants is equivocal. Whereas a study from the USA did not find a significant difference on neurodevelopmental outcome assessed at 18–22 months' corrected age between extremely preterm infants with low-grade IVH compared to those without hemorrhage [7], a study from Australia denoted a negative impact on brain cortical volume, developmental scores and neurosensory system at 2–3 years' corrected age [8].

IVH originates in the germinal matrix, a highly cellular and extensively vascularized region, which is the source of future neuronal and glial cells of the immature brain [5]. IVH may result in a decline of cerebral growth [9], direct parenchymal damage and free iron toxicity, contributing further to IVH-mediated brain damage [10]. However, recent findings from brain magnetic resonance imaging (MRI) studies led to the assumption that neurodevelopmental disability is primarily associated with impaired neural connectivity rather than cell death alone [11]. White matter (WM) abnormalities as defined by lower fractional anisotropy in MR diffusion tensor imaging at term-equivalent age (TEA) have been found in preterm infants with IVH [12–14].

Whereas the understanding of IVH origin and damage has made remarkable progress together with the promising biomarker tool MRI, there are only few evidence-based measures to reduce the risk of IVH such as fetal lung maturation, late cord clamping [15, 16] or early prophylactic indomethacin [17]. Moreover, except for shunt insertion to drain cerebrospinal fluid in infants with posthemorrhagic hydrocephalus and possibly the removal of blood clots in infants with high-grade IVH [18, 19], there is no treatment for established IVH and no medical therapies exist to ameliorate the neurodevelopmental sequelae of IVH.

Potential Benefits and Risks of Erythropoietin in Preterm Infants

Apart from stimulating the production of red blood cells, recombinant human erythropoietin (rEPO) has been shown to exert neuroprotective action in a variety of animal models with brain damage [20]. Administration of rEPO even several days after the insult can enhance neurogenesis and oligodendrogenesis and promotes the recovery of neurological function weeks to months after the insult [21]. Of interest, long-term treatment with rEPO after an insult in the very immature rat brain induced the recovery of WM microstructures and of connectivity as well as somatosensory cortical function without effects on the total brain volume [22]. Observational data from preterm infants who suffered from IVH and who were treated with rEPO to prevent red blood cell transfusions showed improved long-term neurodevelopmental outcomes when assessed at 3 years of age or more [23]. As they received rEPO within days or weeks after the insult, the proposed mode of action of rEPO is thought to be the facilitation of repair, the sustainment of neuronal growth and differentiation after brain injury, rather than protection against damage [24].

rEPO has proven safe in three decades of randomized controlled trials (RCT) evaluating its effect on neonatal erythropoiesis [25] and has gained approval for the use in infants by the regulatory authorities of the USA (FDA), the European Union (EMA) and Switzerland (Swissmedic). Meta-analyses combining early and late rEPO administration to prevent anemia of prematurity have raised concerns about increased rates of severe retinopathy of prematurity associated with the prolonged use of rEPO [26]. Safety issues of high-dose rEPO aimed at crossing the blood-brain barrier in preterm infants also remain a topic in recent investigations [27]. The eagerly awaited safety data from the first large phase II double-masked RCT using high-dose rEPO as a neuroprotective agent given shortly after birth (3 × 3,000 U/kg body weight (BW) rEPO or NaCl 0.9% within the first 36 h of life) to 443 very preterm infants describe no relevant differences between both groups regarding short-term outcomes, including mortality, retinopathy of prematurity and IVH incidence (ClinicalTrials.gov identifier: NCT00413946) [28]. A qualitative and quantitative MRI was performed in a subset of patients at TEA. The MRI findings show that early high-dose rEPO administration resulted in less WM and gray matter injury and in improved WM microstructure [29, 30]. Neurodevelopmental follow-up of the study patients will demonstrate whether these promising MRI findings will translate into improved long-term outcomes [31]. Since the 2-year outcome assessment is limited in predicting later cognitive functions and has been considered recently as a proof of safety rather than an efficacy milestone [32], we expect that the 5-year follow-up tests will give answers as to the clinical and neuroprotective efficacy of early high-dose rEPO in very preterm infants which cannot be provided by the 2-year examinations.

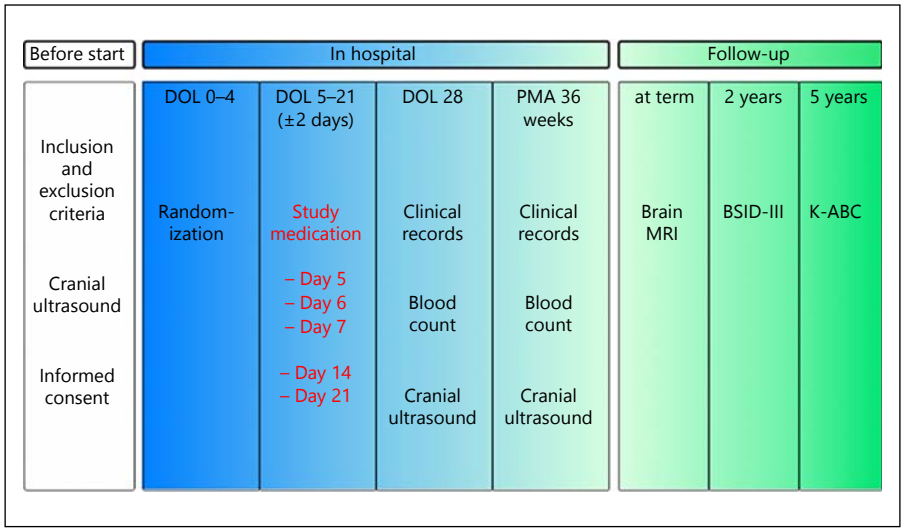

Fig. 1. Course of EpoRepair trial.

Open Questions

Does rEPO administered to preterm infants with IVH improve neurodevelopmental outcome at school age? This is being suggested by data from a retrospective analysis [23] but the question has not been addressed in an RCT. How is the structural brain damage at TEA in preterm infants with IVH, as assessed by MRI, influenced by early rEPO administration and how are these changes related to neurodevelopmental outcome at school age?

Study Summary and Discussion

The EpoRepair trial (Erythropoietin for the Repair of Cerebral Injury in Very Preterm Infants) is an international, multi-center, 1:1 randomized, double-blind, and placebo-controlled clinical trial which aims to evaluate the effect of high-dose rEPO on neurocognitive outcomes of very preterm infants suffering from established IVH. In total, 120 very preterm infants fulfilling the inclusion criteria have to be enrolled to achieve a target sample size of n = 100 for the secondary end point 'MRI at TEA' and to achieve a target sample size of n = 80 for the primary outcome at 5 years of age (for the sample size calculation, see below). The inclusion criteria are as follows: (1) GA at birth <32 weeks or birth weight <1,500 g, (2) diagnosis of IVH (grade II–IV) assessed by cranial ultrasound according to Papile et al. [4] and (3) chronological age <8 DOL.

The study treatment consists of the intravenous administration of rEPO (Epoetin beta®, Roche, Switzerland) with 2,000 IU/kg BW/dose or of physiological saline starting at DOL 5 (±2 days) and repeated 24 h and again 48 h later, with all 3 doses being considered for loading. A further 2 doses are scheduled for maintenance, at 1 week and 2 weeks after the last loading dose (DOL 14 and DOL 21 ±2 days, respectively). The detailed study schedule is given in figure 1. Previous studies in preterm and term infants found 1,000 and 2,500 IU rEPO/kg BW per dose given intravenously well tolerated and sufficient to produce plasma concentrations that are neuroprotective in animals [33, 34]. In the recently completed first large high-dose rEPO trial in very preterm infants, 3,000 IU rEPO/kg BW per dose given intravenously were safe [28] and resulted in promising brain MRI findings [29, 30]. In terms of a pragmatic approach, and also with the aim to add further data with regard to the optimal neuroprotective dosing in very preterm infants, we opted for an intermediate dosage, namely for 2,000 IU/kg BW.

The primary end point of our study is the composite intelligence quotient (IQ, continuous outcome) at the age of 5 years. Normal overall developmental outcome at this age will be a secondary end point (binary variable). The composite IQ will be measured using the Kaufmann Assessment Battery for Children (K-ABC) [35, 36]. Children with hearing or verbal handicaps will be assessed in addition by the Snijders-Oomen nonverbal intelligence test (SON-R) [37]. Overall developmental outcome will be determined by neurological and formal psychological examination and is classified as normal if IQ >84 and without one or more of the following: motor impairment, cognitive impairment, behavior problems, poor general health, severe hearing loss, or bilateral blindness [38].

Other secondary end points are as follows: (1) global injury score, WM and gray matter injury scores assessed on T1- and T2-weighted images (semiquantitative) [29] and fractional anisotropy using tract-based spatial statistics (quantitative) [30], both in brain MRI at TEA, (2) overall severity score of cranial ultrasound findings from birth to PMA 36 weeks as published elsewhere [39] (3) Bayley Scales of Infant and Toddler Development (BSID-III) at 2 years of corrected age [40], including incidence of visual, hearing and motor impairment and (4) mortality.

The alternative hypothesis for all end points is improvement with regard to the end point in the EPO group. The null hypothesis for all end points is no improvement with regard to the end point in the EPO group compared to the control group. Although the study hypotheses are one-sided, the tests, however, will be two-sided, yielding corresponding confidence intervals and, accordingly, information about the direction of a potential difference between the control and EPO groups. The significance level alpha is 0.05.

The statistical analysis will be done on the following levels: (1) confidence intervals will be determined for difference of IQ and other continuous outcomes between the two groups and p values of the corresponding t tests, (2) confidence intervals will be determined for risk differences and corresponding p values for binary outcomes, (3) we will adjust for study centers, taking into account possible center effects, (4) linear and logistic regression will be used to adjust for additional relevant confounding variables with proven impact on outcome (e.g. GA and BW) and (5) multiple imputation will be used to adjust for missing outcomes due to death or dropout [41].

The sample size calculations were based on the following considerations and assumptions. Information about the effect size and the standard deviation (SD) of the primary end point (IQ outcome at age of 5 years) can be derived from only one observational study presented by Neubauer et al. [23], who investigated the effect of rEPO treatment in preterm infants on composite IQ at school age. The authors included in their study all grades of IVH, including the lowest grade, IVH I°. The diagnosis of IVH I°, however, may be missed or even overestimated in very preterm infants [42]. Neubauer et al. [23] reported no difference regarding the composite IQ at 10 years between rEPO-treated and untreated infants without IVH. Thus, we decided to exclude infants with the diagnosis of IVH I° from our study to avoid bias from misdiagnosis. For the relevant group of children who suffered IVH, Neubauer et al. [23] reported an effect size of 23 (SD = 21, $p < 0.01$) between rEPO-treated infants (IQ = 90.3) and untreated infants (IQ = 67.0). Given that the vast majority of children remain on their 5-year IQ trajectory, and that there is good agreement between classification of cognitive abilities at 5 and 11 years of age [43], we used this continuous outcome parameter (effect size of 23) for power analysis based on a X^2 t test assuming a significance level of alpha = 5%, SD = 21 of the outcome and a 1:1 randomization. As a result, we obtained a required total sample size of n = 28 (for both groups together) and of n = 38 for a power (1 – beta) of 80 and 90%, respectively. When assuming a smaller effect size of 10 (instead of 23 when considering the retrospective study design of Neubauer et al. [23]), an SD of 15 (instead of 21 because IVH °I is excluded in our study group to avoid misdiagnosis leading to a sample which is less heterogeneous with regard to the primary outcome) and a power of 80%, the required total sample size amounts to n = 72 for the primary end point at 5 years of age.

Based on the only available data of Neubauer et al. [23] and on the above-mentioned reduction of the assumed effect size to 10 and of the SD to 15, we set the target sample size for the secondary end point 'MRI at TEA', at n = 50 for rEPO and n = 50 for placebo. Given an expected 20% loss to follow-up until 5 years, a sample size of n = 80 will meet the primary end point. This number is congruent with the result of the power analysis presented above. Hence, to achieve the target sample size of n = 100 for the end point 'MRI at TEA' and assuming early loss of 15% due, for example, to death in this high-risk patient population, at least n = 120 preterm infants with IVH II–IV will have to be enrolled in this trial. Accordingly, if early loss exceeds 15%, more infants will need to be enrolled to meet the target sample size of n = 100 for the secondary end point 'MRI at TEA'.

Primarily, it was planned to fill the placebo (physiological saline) in the same type of syringes as those manufactured for single-dose usage of rEPO available from various pharmaceutical companies. This was considered as the most convenient process for blinding, long-term storage and compliance. However, intense negotiations with representatives of various pharmaceutical companies, different hospital pharmacies and research service providers revealed insurmountable obstacles averting this strategy. After considering alternative strategies, it was decided to provide the study medication in new syringes for blinding. According to product information for rEPO (e.g. from Roche), only plastic materials should be used. Since the rEPO stability in vials other than those shipped

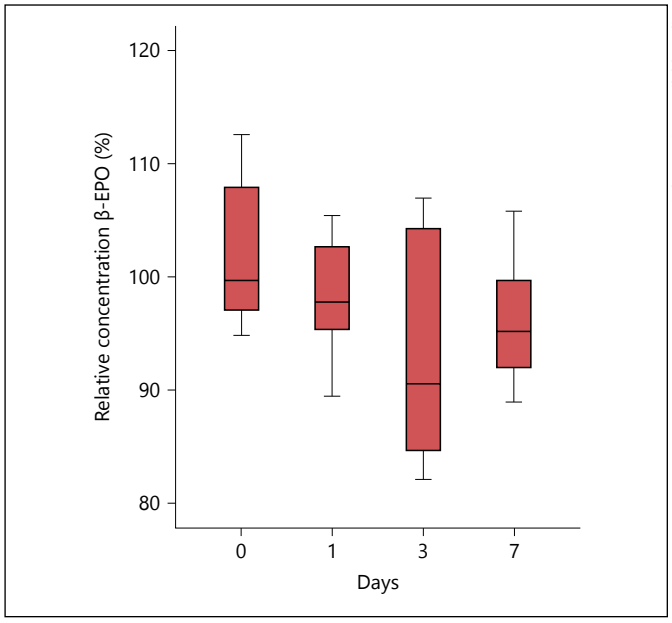

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Fig. 2. Stability of rEPO in plastic syringes. Concentrations of rEPO (Recormon) are plotted to days of storage and are given relative to day 0. Data are presented as box (interquartile range) and whisker (5–95% range) plots. No significant differences were noted between days of storage.

by the manufacturer has caused some concern [44–46], we performed 6 independent experiments to evaluate rEPO stability after storage for variable durations at 4°C. For each time point the complete content of one Recormon® PS 3,000 IU/0.3 ml syringe (Roche) was diluted in 1.2 ml NaCl 0.9% prefilled syringes (2 ml Luer lock; Codan, Lensahn, Germany) and locked with a Combi-Stopper (Arcomed, Regensdorf, Switzerland). After storage of 0, 1, 3, or 7 days at 4°C, 0.5 ml was ejected in a plastic tube containing 49.5 ml NaCl 0.9% (1:100 dilution), of which 10 µl was measured in triplicate with a Quantikine IVD Human Epo ELISA (R&D systems) according to the manufacturer's recommendations. As shown in figure 2, the rEPO stability did not decrease significantly when diluted in NaCl 0.9% and stored at 4°C in plastic syringes for up to 1 week. Statistical significance was determined using the matched pairs test. Student's t test was performed for each pair of data separately. $p < 0.05$ was considered significant.

The study has been approved by the leading ethics committee at the University of Zurich, Switzerland (KEK-ZH 2012-0388) and by the Swiss Regulatory Authority, the Swiss Agency for Therapeutic Products (Swissmedic 2013DR3204). In Germany the study has been approved by the leading ethics committee in Berlin and by the Federal Institute for Drugs and Medical Devices (EudraCT No. 2014-000612-34). The approval for Austria is currently in progress. Written informed consent is required from parents or caretakers. The recruitment for Switzerland began in April 2014 and enrolment is calculated to be about 3 years. It is expected that large study sites with 120–200 infants <1,500 g BW per year (Berlin, Berne, Lausanne, Vienna, Zurich) will each contribute 15–20 study patients and small study sites with 50–120 infants <1,500 g BW per year (Aarau, Basel, Chur, Freiburg, Hannover, Tuebingen, St. Gallen) will each contribute 5–10 study patients (ClinicalTrials.gov identifier: NCT02076373.appro).

Appendix

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Disclosure Statement

All EpoRepair Investigators confirm that they have no conflicts of interest to declare.

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