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Original Article

Erythropoietin and Hypothermia for Hypoxic-Ischemic Encephalopathy

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ABSTRACT

BACKGROUND: Erythropoietin is neuroprotective in animal models of neonatal hypoxic-ischemic encephalopathy. We previously reported a phase I safety and pharmacokinetic study of erythropoietin in neonates. This article presents the neurodevelopmental follow-up of infants who were enrolled in the phase I clinical trial. **METHODS:** We enrolled 24 newborns with hypoxic-ischemic encephalopathy in a dose-escalation study. Patients received up to six doses of erythropoietin in addition to hypothermia. All infants underwent neonatal brain magnetic resonance imaging (MRI) reviewed by a single neuroradiologist. Moderate-to-severe neurodevelopmental disability was defined as cerebral palsy with Gross Motor Function Classification System levels III-V or cognitive impairment based on Bayley Scales of Infant Development II mental developmental index or Bayley III cognitive composite score. **RESULTS:** Outcomes were available for 22 of 24 infants, at mean age 22 months (range, 8-34 months). There were no deaths. Eight (36%) had moderate-to-severe brain injury on neonatal MRI. Moderate-to-severe disability occurred in one child (4.5%), in the setting of moderate-to-severe basal ganglia and/or thalamic injury. Seven infants with moderate-to-severe watershed injury exhibited the following outcomes: normal (three), mild language delay (two), mild hemiplegic cerebral palsy (one), and epilepsy (one). All 11 patients with a normal brain MRI had a normal outcome. **CONCLUSIONS:** This study is the first to describe neurodevelopmental outcomes in infants who received high doses of erythropoietin and hypothermia during the neonatal period. The findings suggest that future studies are warranted to assess the efficacy of this new potential neuroprotective therapy.

Keywords: neonatal encephalopathy, hypoxic-ischemic encephalopathy, neuroprotection, neurodevelopmental outcomes, erythropoietin

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Introduction

Perinatal hypoxic-ischemic encephalopathy (HIE) is an important cause of neonatal encephalopathy and occurs in one to three per 1000 term births,[1,2] affecting up to 12,000 infants each year in the United States. Therapies remain limited. Hypothermia initiated within 6 hours of birth provides modest improvements in outcome.[3-7] Yet despite this therapy, over 40% of infants with moderate-to-severe

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HIE die or suffer moderate-to-severe disabilities including cerebral palsy, intellectual impairment, and epilepsy. New neuroprotective therapies are needed to further reduce the unacceptably high risk of adverse outcomes after HIE.

The hematopoietic cytokine erythropoietin (Epo) has neuroprotective and neuroregenerative effects in the brain.[8-13] High doses of Epo administered to neonatal rodents after hypoxic-ischemic brain injury result in improved histologic and functional outcomes and enhanced neurogenesis and repair.[14-20] In a nonhuman primate model of HIE in which hypothermia alone did not significantly improve outcomes, the combined treatment of Epo and hypothermia resulted in a significantly lower rate of death or moderate-to-severe cerebral palsy than did treatment with saline alone (0% versus 43%, $P < 0.05$).[21] Compared with animals treated with saline, those that received both Epo and hypothermia also demonstrated improved long-term motor and cognitive responses, enhanced cerebellar growth, and improved fractional anisotropy on early diffusion tensor imaging.[21]

Two clinical trials reported that human infants with HIE who received five to seven doses of Epo during the first week of age, in the absence of hypothermia, experienced improved neurological outcomes.[22,23] After hypothermia became the standard of care in the treatment of HIE, we evaluated the safety and pharmacokinetics of combined Epo and hypothermia therapy in a phase I trial and found that multiple doses of Epo ranging from 250 to 2500 U/kg IV appeared safe in the neonatal period.[24] However, longer term outcome data have yet to be reported in cooled infants who received high-dose Epo as a neonate. Therefore, we present the neurodevelopmental outcomes of infants with HIE who received high doses of Epo and hypothermia therapy during the first week of age.

Study design

We previously reported a phase I safety and pharmacokinetic study of Epo in neonates.[24] The current article presents the neurodevelopmental follow-up of infants who were enrolled in the phase I clinical trial. In an open-label dose-escalation study,[24] 24 newborns ≥37 weeks of gestational age undergoing hypothermia for HIE received one of the following four Epo doses IV: 250 (n = 3), 500 (n = 6), 1000 (n = 7), and 2500 U/kg per dose (n = 8). We studied these doses to determine which would achieve target plasma Epo levels based on available data from animal studies. We administered up to six doses of Epo every 48 hours, starting by 24 hours of age. Each patient met inclusion and exclusion criteria for encephalopathy and perinatal depression as previously described.[24,25] All patients also underwent standard 72 hours of hypothermia therapy using either whole body (n = 21) or head (n = 3) cooling. All patients received a brain magnetic resonance imaging (MRI) at the completion of hypothermia therapy as part of routine clinical care. A study neuroradiologist (A.J.B.) who was blinded to patient outcomes interpreted the MRI studies using a previously validated scoring system.[26] The MRI was classified as normal, abnormal with a predominant watershed pattern of injury, or abnormal with predominant basal ganglia and/or thalamic injury. Severity of injury was dichotomized as being either moderate and/or severe or mild and/or normal as previously described.[27] The study received institutional review board's approval at each of five participating hospitals.

After hospital discharge, patients were evaluated in the high-risk infant follow-up programs of each of the five study sites, as part of routine clinical care. During these visits, patients were evaluated for neurodevelopmental abnormalities: cerebral palsy, tone abnormalities, motor delay, language delay, and presence of seizures. The Bayley Scales of Infant Development (Bayley) II or III was performed in 16 patients at median age 24.4 months (range, 13-34 months). The eight patients who did not receive Bayley testing were either enrolled at a site where Bayley testing is not performed routinely (n = 5) or did not receive Bayley testing as part of their follow-up assessment (n = 3). We defined moderate-to-severe disability as either a clinical diagnosis of cerebral palsy with Gross Motor Function Classification System (GMFCS) III-V or moderate-to-severe cognitive delay based on Bayley II MDI of <70 or Bayley III cognitive composite score of <80. Mild impairment was defined as cognitive or language delays requiring referral to early intervention services, epilepsy, or abnormal neurological examination without a diagnosis of cerebral palsy or functional impairment.

Results

Twenty-four of 26 infants consented to the study. Hypotonia, lethargy, and poor suck were the most common signs of encephalopathy (Table 1). Fifteen infants (63%) had a 10-minute Apgar score of ≤5, and mean arterial or venous cord pH was 6.87 (S.D. = 0.14). Almost half of infants (45.8%) were delivered via emergent cesarean section. A sentinel event occurred in seven patients (29%), including placental abruption (four), uterine rupture (two), and prolapsed cord (one). Over half (n = 13) had either clinical (n = 9) or electrographic (n = 7) seizures during the hospital stay. Average length of hospitalization was 13.5 ± 7.2 days (range, 6-36 days).

Patients received a mean of 4.8 (±1.2) Epo doses (range, 2-6 doses). Patients who did not receive all six doses of study drug were either discharged to home before the last dose (10), lost IV access (four), or had a protocol violation (one). All doses of Epo were tolerated well with no apparent adverse effects. There were no neonatal deaths, and the frequency of systemic complications was not statistically different from that reported in historical controls who received hypothermia alone.[24,25]

MRI findings

Brain MRI performed at a median age of 6 days (range, 4-13 days) revealed no abnormalities in 13 of 24 patients (54%). Of the 11 who had MRI evidence of brain injury, nine had injury predominantly in the watershed distribution, one had basal ganglia predominant injury, and one had a focal arterial infarction. Moderate-to-severe brain injury was present in eight infants (seven watershed and one basal ganglia and/or thalamus), whereas mild injury was observed in three infants (two watershed and one focal arterial infarction).