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Original article

# Short-term effects of erythropoietin on neurodevelopment in infants with cerebral palsy: A pilot study

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**Abstract**

*Objective:* Cerebral palsy (CP) is a disabling condition characterized by the motor impairment, which is difficult to be ameliorated. In the brain of infants with CP, there are persistent pathomechanisms including accentuated neuroinflammation. Since erythropoietin was demonstrated to have neuroprotective effect via anti-inflammatory and anti-apoptotic properties, we hypothesized that the administration of recombinant human EPO (rhEPO) could help children with CP, especially young infants. *Materials and method:* We investigated the therapeutic efficacy of rhEPO for infants with CP, who had been undergoing active rehabilitation in hospitalized setting to eliminate treatment bias. Twenty infants with CP were randomly divided into EPO or control group equally. We compared the changes in the Gross Motor Function Measure (GMFM) and the Bayley Scales of Infant Development-II (BSID-II) scores during one month of hospitalization between two groups. *Results:* The improvements after 1 month on the GMFM A and GMFM total scores differed significantly between the groups ($p = 0.003$, $p = 0.04$, respectively). However, the changes after 6 months were not different between the two groups. The scores of BSID-II did not show any differences at 1-month and 6-months post-treatment. *Conclusion:* These results indicated that rhEPO could have therapeutic efficacy for infants with CP during the active rehabilitation and anti-inflammation was suggested to be one of its therapeutic mechanisms.


*Keywords:* Cerebral palsy; Recombinant human erythropoietin; Anti-inflammatory effect; Neurodevelopment

## 1. Introduction

Cerebral palsy (CP) is a group of disorders involving impaired development of movement and posture, which are attributed to the various non-progressive damages in the brain of developing fetus or infants [1]. Children with CP have disabilities not only from motor impairment but also from accompanied disorders in other functions including sensation, cognition, communication, vision, and behavior. Although various managements have been tried to improve clinical features of CP, most of them are complementary and there has been no medical treatment which can repair the basic pathology of CP at present [2].

Recent studies revealed active pathomechanisms in the brain of children with CP [3], and altered inflammatory response would be one of the most representative

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characteristics [4]. Persistent neuroinflammation in CP brain was suggested as a target of therapeutic opportunity [5], yet no active method focused on this approach has been reported to our knowledge. Accentuated apoptosis is known to be another important mechanism in CP [6], and anti-apoptotic agents could reverse the apoptosis during a therapeutic time window after hypoxia-induced injury [7]. Among the molecules, recombinant human EPO (rhEPO) is most acceptable, based on its clinical availability and safety with least side effect profiles even in it use for infants [8,9]. In animal studies, rhEPO was found to have neuroprotective effects on experimentally induced cerebral ischemia [10], hyperoxia-induced brain cell death [11], and lipopolysaccharide-induced white matter injury in neonates [12] due to the anti-inflammatory and anti-apoptotic characteristics [13]. In addition, rhEPO was also reported to contain angiogenic effects [14], and it increased neurogenesis in patients with neonatal stroke [15]. Moreover, administrations of rhEPO to extremely preterm infants at the neonatal intensive care unit improved neurodevelopmental outcomes [16].

However, no clinical study was performed to assess the adjuvant therapeutic efficacy of rhEPO during the rehabilitation of infants with CP. Here, we hypothesized that rhEPO could improve the motor development in infants with CP by its neurotrophic effects especially during the intensive rehabilitations. The efficacy of rhEPO on the short-term neurodevelopmental outcomes were assessed during the intensive rehabilitation of hospitalized CP infants with known origin of brain insult.

## 2. Materials and methods

### 2.1. Open-label, random controlled study

#### 2.1.1. Subjects

Enrolled infants with CP were less than 1 year old as corrected age. They were admitted to the Department of Rehabilitation Medicine of Bundang CHA Medical Center for the intensive rehabilitation from March 2009 to May 2011. Inclusion criteria were: (1) no known genetic disorder; (2) identifiable brain lesion by MRI and/or known perinatal history that could explain the cause of abnormal neurodevelopment; (3) clinically diagnosed as CP with delayed motor development and abnormal muscle tone and movement; (4) baseline hemoglobin level <13.5 g/dL; and (5) no problem interfering with the rehabilitation during the hospitalization. We used high-resolution chromosomal analysis and multiplex ligation-dependent probe amplification (MLPA) analysis to exclude the possibility of genetic disorder. All subjects were scanned using a 3T GE Signa System (General-Electric, Milwaukee, WI, USA) for conventional MRI, including sequences of T1-weighted, T2-weighted, Fluid Attenuated Inversion Recovery (FLAIR), Gradient Echo (GRE), and Diffusion Tensor Imaging (DTI). We enrolled a total of 20 subjects, who were randomized into two groups, the study group treated with rhEPO; rhEPO group ($n = 10$), and the other being a control group ($n = 10$). The parents of the subjects provided the written informed consents. The study was not blinded because it was the first pilot trial for fragile infants with CP. The study was approved by the Institutional Review Board at Bundang CHA Medical Center.

#### 2.1.2. Rehabilitation intervention

All infants, randomized to the rhEPO and control groups, underwent the identical intensive rehabilitation therapies, according to our protocol for infants with CP. All infants received the physical and occupational therapies twice per day on weekdays and once per day on weekends for 1 month. Rehabilitation therapy was designed to facilitate normal movements by inducing each patient to participate actively in moving, thus enhancing the functional control, righting reaction, balance, grasp and endurance. We also provided these patients with experiences of the normal movements and with cognitive and perceptual stimulations. The parents of each subject were educated with methods to care for their infants, and all parents complied with given instructions.

#### 2.1.3. rhEPO administration

Randomized patients to the rhEPO group were administered with 250 IU/kg of rhEPO, subcutaneously twice a week. Higher dosage than that used for patients with anemia was determined in order to it may penetrate the blood–brain barrier (BBS). It was reported that EPO was detectable in brain by administering 250 IU/kg of rhEPO via subcutaneous or intraperitoneal injection, although the concentration was low [17]. We measured the complete blood cell counts every week until the discharge to avoid erythrocytosis. The rhEPO administration was stopped, if the hemoglobin level increased to 15 g/dL. We recommended that participants in this group to avoid iron supplements during rhEPO treatment. Over the 1-month treatment period, a mean of 7.2 injections (1800 IU/kg) of rhEPO (range, 5–9 injections, total amount 1500–2500 IU/kg) were administered in the rhEPO group.

#### 2.1.4. Evaluation and measurement of outcome

All subjects underwent the neurological examinations at admission and discharge by specialists in the pediatric rehabilitation medicine. Patients were classified according to the Gross Motor Functional Classification System for CP (GMFCS) [18], and their type of tonus abnormality. Developmental outcomes were assessed with Gross Motor Function Measure 88 (GMFM-88) [19] and the Bayley Scales of Infant Development-II