Journal of Clinical Neuroscience 21 (2014) 1283–1287

Contents lists available at ScienceDirect

Journal of Clinical Neuroscience

journal homepage: www.elsevier.com/locate/jocn

Review

Neuroprotection with erythropoietin in preterm and/or low birth weight infants

Jie Zhang, Qiuxia Wang, Hong Xiang, Yue Xin, Ming Chang, Hongyan Lu *

Department of Pediatrics, The Affiliated Hospital of Jiangsu University, 438 Jiefang Road, Zhenjiang 212001, Jiangsu Province, PR China

ARTICLE INFO

Article history:
Received 5 July 2013
Accepted 27 October 2013

Keywords:
Brain injury
Erythropoietin
Low birth weight infants
Neonates
Neurodevelopmental outcome

ABSTRACT

Neonatal brain injury caused by extreme prematurity remains a great challenge for prevention. Erythropoietin (EPO) has shown neuroprotective effects in a series of neonatal experimental models and recent clinical trials of premature infants. In this meta-analysis of seven clinical trials, EPO was associated with a highly reproducible reduction in the risk of neurodevelopmental disability in preterm infants. However, there was no difference in the risk for morbidity, cerebral palsy, visual deficit, severe hearing deficit, necrotizing enterocolitis, intracranial hemorrhage and patent ductus arteriosus. The use of EPO, to some extent, is associated with reduction in neurodevelopmental disability in preterm infants. More double blind randomized controlled trials are needed to establish the best therapeutic approach for neuroprotection in preterm infants.

1. Introduction

Preterm birth rates have been reported to range from 5% to 7% of live births in some developed countries, but are estimated to be substantially higher in developing countries [1]. These figures appear to be rising [2]. Children who are born prematurely have a high risk of neurodevelopmental delay [3,4]. Neurodevelopmental impairment (neurosensory abnormality including cerebral palsy, deafness, blindness, and/or Mental Developmental Index score of <70) is present in 36% to 48% of survivors [5,6]. These deficits impart a significant burden to the children, their families, and society. Given the high incidence of survival with neurodevelopmental sequelae, physicians have been searching for effective strategies to prevent or minimize the long-term consequences of neonatal brain injury of prematurity.

Erythropoietin (EPO), which was originally identified for its role in erythropoiesis, has been used to treat a number of anemic states, including early and late anemia of prematurity [7,8]. Surprisingly, neuroprotection with EPO has also been documented in spinal cord injury, traumatic brain injury, ischemic stroke, and perinatal asphyxia [9].

Successful pilot studies suggested that EPO was both feasible and broadly safe in neonates, supporting further randomized trials. The primary objective of this systematic review was to evaluate the efficacy and safety of EPO used for neuronal development protection, including results from recent trials.

2. Methods

2.1. Studies

For this review, both randomized and quasi-randomized (for example, randomization based on day, date, or hospital number) clinical trials of EPO used for neuronal development protection were included. Cohort studies, retrospective studies, case series, case reports, letters to editors that did not contain primary data, editorials, review articles and commentaries were not included, but were explored to identify potential new studies. Multiple reports of primary studies were reviewed to identify all relevant outcomes for this article.

2.2. Participants

Preterm (<37 weeks) and/or low birth weight (<2500 g) neonates were considered eligible for inclusion.

2.3. Intervention

Studies that investigated EPO treatment *versus* placebo or no intervention were eligible for inclusion.

* Corresponding author. Tel.: +86 511 8508 2260.
E-mail address: lhy5154@163.com (H. Lu).

http://dx.doi.org/10.1016/j.jocn.2013.10.040
0967-5868/

2.4. Outcomes

The outcomes for this review were mortality, neurodevelopmental disability among survivors, cerebral palsy, cognitive (Mental Developmental Index <70) delay, psychomotor (Psychomotor Developmental Index <70) delay, visual deficit, severe hearing deficit, necrotizing enterocolitis, intracranial hemorrhage, and patent ductus arteriosus.

2.5. Literature search

The Cochrane Central Register of Controlled Trials (CENTRAL *The Cochrane Library* 2012, Issue 2) was searched to identify relevant randomized and quasi-randomized controlled trials. MEDLINE was searched for relevant articles published from 1966 to November 2012 using the following Medical Subject Headings (MeSH) terms or text words: (exp Erythropoietin/OR erythropoietin:.mp. OR rhuepo.mp.) AND (neurodevelopment/OR neuroprotection/OR neurobehavioral development/OR neurological development/OR neural development) AND (infant, newborn/OR infant, low birth weight/OR infant, very low birth weight/OR infant, premature/OR exp Infant, Premature, Diseases) OR (neonate: OR prematur*: OR newborn:).mp. OR newborn infant [age limit]AND (clinical trial.pt. OR Randomized Controlled Trials/OR random: OR rct OR rcts) OR (blind OR blinded OR placebo:).mp. OR (review.pt. OR review, academic.pt.) AND human. EMBASE was queried from 1980 to November 2005 and CINAHL from 1982 to November 2012 using the following MeSH terms or text words: Erythropoietin/OR erythropoietin: OR epo OR epogen OR epoetin: OR (rhuepo).mp. AND (neurodevelopment/OR neuroprotection/OR neurobehavioral development/OR neurological development/OR neural development) AND exp Infant, Premature, Diseases/OR infant, newborn/OR infant, low birth weight/OR infant, very low birth weight/OR infant, premature/OR (neonate: OR newborn: OR prematur*:).mp. OR newborn infant. In addition the bibliographies were manually searched. No language restrictions were applied. Abstracts published from the Pediatric Academic Societies' Meetings and the European Society of Pediatric Research Meetings (published in Pediatric Research) were hand searched from 1980 to April 2012.

2.6. Data extraction

All abstracts and published studies identified as potentially relevant by the literature search were assessed for inclusion by two review authors. Each author extracted data separately on a data extraction form. The information was then compared and differences were resolved by consensus. One review author (A.O.) entered data into RevMan 5.1 Software (Cochrane Collaboration, Oxford, UK) and the other (S.A.) cross-checked the printout against his own data extraction forms and any errors were corrected. For the studies identified in abstract form, the primary author was contacted to obtain further information.

2.7. Quality assessment

The quality of included trials was evaluated independently by the review authors using the following criteria: blinding of randomization, blinding of intervention, blinding of outcome measure assessment, and completeness of follow-up.

2.8. Data analysis

Data on efficacy were collected from studies that reported childhood outcomes. A typical effect size was calculated and reported as pooled relative risk (RR) and number needed to treat to benefit or harm as appropriate with 95% confidence interval. Studies were weighted in all meta-analyses according to inverse of variance of the outcomes of interest in individual studies. All analyses (fixed effects model) were performed using Revman 5.1 software. The χ^2 test was applied to detect between-study heterogeneity and I^2 values were calculated to assess statistical heterogeneity. Statistical corrections were not employed to adjust for multiple analyses.

3. Results

Twenty-one reports were evaluated for eligibility. Five retrospective studies, four case series, and five prospective cohort studies were excluded. Eight reports of seven clinical trials were selected for inclusion in this review.

3.1. Clinical heterogeneity assessment among included studies

A total of 523 patients were randomized in the included trials. A detailed description of the studies included is given in Table 1 [10–17].

3.2. Primary outcome: Neurodevelopmental disability in childhood

Data on this primary outcome were reported in four studies. There was a significant reduction in the risk of neurodevelopmental disability in infants who received EPO compared to controls (four studies, 297 participants, over effect $Z = 2.01$ [$p < 0.05$]; pooled RR = 0.77; test of heterogeneity $p = 0.5$ and $I^2 = 0\%$) (Fig. 1).

3.3. Effectiveness outcomes

There was no difference in the risk of morbidity, cerebral palsy, Mental Developmental Index <70, Psychomotor Developmental Index <70, visual deficit, severe hearing deficit, necrotizing enterocolitis, intracranial hemorrhage or patent ductus arteriosus between infants who received EPO and controls (Fig. 2).

4. Discussion

Preterm infants are at a high risk for brain injury and subsequent neurodevelopmental problems. This meta-analysis of seven eligible trials in infants confirms that EPO was associated with a reduced risk of the overall outcome of neurodevelopmental disability in infancy. There was no difference in the risk of morbidity, cerebral palsy, visual deficit, severe hearing deficit, necrotizing enterocolitis, intracranial hemorrhage and patent ductus arteriosus.

EPO is a 34 kD glycoprotein with four carbohydrate residues, and was originally purified in the 1970s [18]. The brain effects of EPO are proposed to involve a heteromeric receptor comprising the classical erythropoietin receptor (EPOR). Most neurons are likely to express high levels of EPOR [19]. Binding of exogenous or endogenous EPO with EPOR leads to conformational changes in EPOR protein and the signaling protein. Activation of EPO signaling pathways can inhibit the process of neurotoxicity, apoptosis, inflammation, cerebral edema and white matter injury while increasing neural regeneration including neurovascular remodeling, neural stem cell proliferation and neurite outgrowth [20–26].

EPO has been shown to have beneficial effects in the central and peripheral nervous system, observed in multiple settings [27–29]. Neonatal recombinant human EPO administration in a novel, clinically relevant paradigm initiated 4 days after a global prenatal hypoxic-ischemic insult in rats rescued neural cells, and induced lasting histological and functional improvement in adult rats [24]. Administration of a single dose of EPO directly after an acute hypoxic event has protective effects against subsequent