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ORIGINAL ARTICLE

Early Erythropoietin Administration does not Increase the Risk of Retinopathy in Preterm Infants

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Key Words
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Background: Erythropoietin (EPO) administration prevents anemia of prematurity and may be associated with a significant increase in the risk of retinopathy of prematurity (ROP) in preterm infants. Nonetheless, early EPO treatment may prevent damage following retinal neovascularization. The aim of this meta-analysis was to elucidate whether EPO administration increases the risk of ROP.

Methods: We searched MEDLINE, PubMed, CINAHL (Cumulative Index to Nursing and Allied Health Literature), and the Cochrane Central Register of Controlled Trials with no language restrictions. Randomized controlled trials that reported the association between EPO treatment in preterm infants and ROP were eligible. All of the included studies were stratified into two groups according to the age of initiation of EPO treatment: before 8 days of age (early EPO), and 8–28 days of age (late EPO).

Results: Thirteen studies were identified that included a total of 1999 preterm infants. EPO administration did not increase the risk of ROP of any stage or Stage $\geq$3 (any relative risk: 0.99, 95% confidence interval: 0.84–1.16, $p = 0.89$; Stage $\geq$3 relative risk: 1.34, 95% confidence interval: 0.90–1.99, $p = 0.15$). This trend remained unchanged in both the early and late EPO groups. There did not seem to be any evidence of publication bias for outcomes as the funnel plots were symmetrical.

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Conclusion: EPO administration did not significantly increase the risk of ROP of any stage reported or Stage ≥3. Further clinical trials investigating the impact of EPO on ROP in premature infants should include all confounding factors to clarify this important issue.

1. Introduction

Several studies have shown that early erythropoietin (EPO) administration is effective in the prevention of anemia and reduces the need for red blood cell (RBC) transfusion in preterm infants.[1–3] Despite the beneficial effects of EPO in preterm infants, a Cochrane review reported that although there was no significant increase in the rate of Stage ≥3 retinopathy of prematurity (ROP) in studies that initiated EPO treatment at <8 days of age.[4] In *post hoc* analysis including all studies regardless of age at initiation of treatment there was an increased risk of ROP in the EPO treatment group. A recent retrospective study also showed that EPO therapy appears to increase the risk of developing and worsening of ROP.[5] Due to the limited benefits and increased risk of ROP, the early administration of EPO was not recommended by several studies[5,6] and the Cochrane review.[4]

ROP is characterized by peripheral retinal ischemia and secondary neovascularization with neuro-vascular degeneration.[7] Thus, one way to reduce the risk of blindness from retinal neovascularization is to prevent the retinal vasculopathy that precedes and causes it. EPO has been reported to be a powerful cytoprotective agent that protects both neurons and vascular cells from apoptosis and mobilizes bone marrow progenitor cells to the peripheral blood stream for vascular repair.[8–10] EPO was also shown to protect developing retinas in an ovine model of endotoxin-induced retinal injury.[11] In addition, the short-term systemic administration of exogenous EPO in the early stages of retinal ischemia was found to improve retinal neuronal function, prevent retinal capillary dropout, and subsequent neovascularization in an animal model of oxygen-induced retinopathy.[9,10]

A recent retrospective analysis of 718 very low birth weight infants showed that early use of EPO did not lead to an increased risk of severe ROP (only Stage 1).[12] The authors speculated that the increase in Stage 3 ROP observed in other studies may be due to the concomitant actions of EPO and high doses of iron.

Furthermore, EPO has been shown to have beneficial neurological effects in recent animal studies, including decreases in hemorrhagic volume, hypoxic-ischemic brain injury, neuronal apoptosis, and neurological deterioration.[13,14] High-dose EPO treatment has been associated with a modest improvement in neurodevelopmental outcomes,[15] and a reduced risk of brain injury on magnetic resonance imaging at a term-equivalent age.[16]

Given the controversial effects of EPO in preterm infants, there is an urgent need to clarify the impact of EPO on ROP before further prospective control trials are conducted to investigate the neuroprotective effects of EPO in these vulnerable preterm infants. Therefore, we conducted this updated meta-analysis of currently available randomized controlled trials (RCTs) and quasi-RCTs to assess the effectiveness and safety of the early initiation of EPO in reducing ROP in preterm and/or low birth weight infants.

2. Methods

2.1. Inclusion criteria

RCTs or quasi-RCTs (i.e., those with an inadequate allocation concealment),[17] which recruited preterm neonates with a gestational age of <37 weeks and/or birth weight <2500 g were included in this meta-analysis. These interventions assessed the effects of EPO versus a placebo or no treatment on ROP.

2.2. Search strategy

MEDLINE (1966 to August 2014), PubMed (1966 to August 2014), and CINAHL (Cumulative Index to Nursing and Allied Health Literature; 1982 to August 2014) databases were searched to identify RCTs. The Cochrane Central Register of Controlled Trials (CENTRAL) was also searched. The following medical subject heading terms and text words were used: (erythropoietin OR epoetin OR rhuepo OR EPO) AND (retinopathy of prematurity OR ROP) AND (low birth weight OR prematurity OR preterm). We restricted the search to human studies, and no language restrictions were applied. Additional information was retrieved via a manual search of references from recent reviews and relevant published original studies.

2.3. Data extraction

Two reviewers (Chou and Lin) independently reviewed each reference identified through the search, scanned the full texts of the relevant studies, applied the inclusion criteria, and extracted data separately on a data abstraction form. The extracted data included baseline characteristics of the included trials, the study drugs, doses, use of a placebo or no treatment, follow up, and loss of follow up. The primary outcome of interest was the number of patients who developed ROP (including ROP of any stage reported and Stage ≥3). One review author (Chou) entered data into Review Manager (RevMan) version 5.0 statistical software (Cochrane Collaboration, Oxford, UK), and the other (Lin) cross-checked the printout against his own data abstraction forms.

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