Erythropoietin may improve the Outcome in Infants with Moderate to Severe Hypoxic Ischemic Encephalopathy

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CONTEXT
Disability is a serious complication of hypoxic ischemic encephalopathy (HIE). At the current time, therapeutic hypothermia has been shown to be effective in reducing the risk of death and neurological impairment – if used in the first 6 h of life. However, evidence is lacking for its efficacy outside this period of time.

Objectives
Zhu et al. aimed "to investigate whether systemic administration of low doses (300-500 U/kg) of recombinant human erythropoietin (EPO) could improve neurodevelopmental outcome at 18 months for infants with moderate or severe HIE" the first 6 h of life.

MATERIALS AND METHODS
This is a multi-center (2 centers) study done in China between August 2003 and January 2007.

Population
The study included infants born at term with birth weight >2500 g with evidence of perinatal asphyxia (apgar score <5 at 5 min or continued need for resuscitation at 10 min) having moderate or severe HIE according to Sarnat staging. Infants with congenital anomalies, hypothermia, trauma, hemorrhage or financial problems were excluded.

Intervention
Recombinat EPO was given in the firsts 48 h of age at a dose of 300 IU/kg at the start of the study and later increased to 500 IU/kg since no side effects were reported. However, no placebo was given to the control group.

Outcome
Death or disability (Mental developmental index <70, presence of cerebral palsy, severe hearing loss or blindness) occurred at 18 months.

Allocation
Randomization method was not explicitly mentioned. It does not seem to be randomized since parents are paying the cost of EPO and no consent was obtained from parents of infants enrolled in the control group.

Blinding
Only outcome assessors were blinded but not parents or treating team.

Follow-up
Total of seven patients dropped out and 3 lost follow-up in the EPO group while 2 and 2 in the control group respectively.

RESULTS
The analysis was performed in 73 infants in the EPO group
and 80 in the control group. No baseline difference was documented. Authors found significant reduction in the rate of disability in the EPO group (relative risk (RR): 0.59 and 95% CI: 0.38-0.93) but no statistically significant effect on mortality (RR: 0.89 and 95% CI: 0.37-2.13). In addition, the rate of combined outcome of death or disability and was also reduced (RR: 0.62, CI: 0.41-0.94). This seemed to be related to the reduction in disability in the infants with moderate HIE (RR: 0.26, CI: 0.09-0.76) treated with EPO but not the ones with severe HIE (RR: 0.70, CI: 0.43-1.15). There was no reported adverse effect of EPO.

**COMMENTARY**

Although there seemed to be major reduction in the long-term outcome (disability), the result of this study should be taken with caution. This study is not randomized. It seems to be a case control study. Only infants of parents who were willing and paying the treatment were enrolled in the EPO group. The group of parents might belong to a better socio-economic status which could contribute to better outcome. In addition, this study was not double-blinded which subjects it to major biases related to co-intervention. Moreover, there was no mention of detailed maternal and neonatal characteristics, severity of cord blood gas and in hospital outcomes (respiratory, cardiovascular, seizure etc.). There was no mention of the intention to treat analysis and contamination with EPO in the control group. It is also worth mentioning that no consistency on the number of infants who were included in the final analysis.

**SUMMARY**

The effect of EPO on disability seems to be very large which might be contributed partially to the possibility that this was not a randomized or blinded study and its effect was actually related to selection bias or co-intervention. Therefore, we cannot recommend adopting the use of EPO as standard treatment to prevent disability in infants with moderate or severe HIE. Furthermore, double-blind multicenter trials are needed.

Abstracted from

Zhu C, Kang W, Xu F, Cheng X, Zhang Z, et al. Erythropoietin Improved Neurologic Outcomes in Newborns With Hypoxic-Ischemic Encephalopathy. Pediatrics. 2009 Aug; 124(2):E218-26. doi: 10.1542/peds.2008-3553. Epub 2009 Jul 27.

**REFERENCE**

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