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# Erythropoietin (Epo) Does Not Improve the Outcome in Neonatal Hypoxic Ischaemic Encephalopathy

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Neonatal hypoxic ischaemic encephalopathy (HIE) is a neurological injury in newborn infants due to a reduction of oxygen and blood flow around the time of birth. The incidence in Ireland is 1.1 per 1,000 births, there are 70 cases annually[1]. Rates in other developed countries are similar. In the US there are 9,000 to 12,000 each year. In many cases, HIE results in death or long-term disability. It is estimated that it accounts for 22% of deaths worldwide.

The hypoxic brain injury causes primary energy failure with a decrease in ATP production. There is anaerobic metabolism, lactic acidosis, cell membrane failure, the influx of calcium and sodium, and varying amounts of cell death. A cascade of inflammatory reactions subsequently take place with the release of pro-apoptotic proteins. Thus the mechanism of cell death changes from early necrosis to later apoptosis. The process continues with impaired neurogenesis, and alteration in synaptogenesis and axonal growth. The key targets for neuroprotection research are modification of the acute inflammation, the apoptotic cell death, and the stimulation of repair mechanisms.

At present, the only effective treatment for newborn infants suffering from HIE is therapeutic cooling (TH)[2]. The hypothermia reduces the brain's metabolic rate, and it modifies the cells programmed for apoptosis mainly by inhibition of caspase activation. It suppresses the inflammatory cascade. It has been estimated[3] that every 1° C decrease in body temperature reduces cerebral metabolism by 7%.

The infant's body temperature is reduced to 33 – 34° C for 72 hours. TH is time-sensitive and must be commenced within 6 hours of the infant's birth. TH was introduced into neonatal clinical practice in 2009. While the TH is an important tool in the management of HIE, it has limitations. TH only helps one in seven babies with HIE. Up to 40% of infants treated with TH still suffer death or handicap.

Over the last two decades, investigators have been examining potential adjuvant therapies that might act in combination with TH to further improve outcomes in infants suffering from HIE. Recombinant human Erythropoietin (Epo) has been put forward as a potential candidate[4]. Epo is primarily known for its haematological functions. It is naturally produced by the peritubular cells of the kidney. PO2 regulates Epo production. The lower the PO2, the greater the secretion of Epo.

Epo has also been found to have neurological effects. It inhibits glutamate release and brain cell death. A preliminary study involving 50 newborn babies found that Epo resulted in less MRI injury, and better function[5].

More recently the HEAL (high dose Epo for asphyxia and encephalopathy) trial was undertaken[6]. The aim was to determine whether multiple high doses of Epo administered to infants with HIE during the first week of life would reduce the risk of death or handicap. Its results were published in the NEJM on July 14th, 2022. The trial recruited 501 term infants undergoing therapeutic hypothermia for moderate or severe HIE across 15 NICUs in the US. It was a double-blind, placebo-controlled RCT. Infants with HIE were administered Epo or placebo. The Epo dose was 1,000 U/kg – five doses – the first dose before 26 hours old, and subsequent doses at days two, three, four, and seven. The control infants were administered saline. In both groups the proportion of infants with moderate or severe HIE was similar (77% and 23% respectively). The primary outcome was death or neurological impairment at 22 – 36 months of age. There were 257 infants in the Epo group and 243 infants in the placebo group.

The main finding in the study is that Epo did not improve the outcome of babies with HIE. The rate of death or neurological disability was 52.5% in the Epo group and 49.5% in the placebo group. The mean number of serious adverse events per infant was higher in the Epo group – 0.86 vs 0.67. There was a higher rate of behavioural anomalies at 2 years in children in the Epo group. There was no difference in the brain MRI findings between the two groups.

The findings of this large, well conducted trial indicate that Epo is not beneficial for infants suffering from HIE. The reasons that it did not work are unclear. One suggestion is that TH and Epo may initiate similar neuroprotective pathways during the acute phase of the HIE injury. In other words, the hypothermia may have minimised any potential benefit from the Epo. Other possible explanations are that Epo administration in the early hours after the asphyxia may have adverse effects, and that later doses would be more effective.

The increased rate of side-effects in the Epo group was unexpected. It was not any specific complication but across a group of side-effects. This is in contrast to the smaller trials in which Epo was found to be safe.

While this study had a negative outcome, there are a number of positive aspects. It highlights the importance of research that will advance the management of neonatal HIE, which is an important cause of morbidity and mortality. It provides an exemplar on how studies about adjuvant therapies for HIE should be conducted. It illustrates the importance of recruitment across multiple neonatal centres in order to obtain adequate numbers of infants quickly when evaluating new adjuvant therapies for HIE.

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