NEUROPROTECTIVE EFFECTS OF ERYTHROPOIETIN ON WHITE MATTER DEVELOPMENT IN PRETERM INFANTS INVESTIGATED WITH TRACT BASED SPATIAL STATISTICS

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Target audience: Researchers and clinicians interested in neonatal MRI and diffusion tensor imaging

Purpose: Diffuse white matter injury is the most prominent brain injury reported in preterm infants and is associated with significant neurodevelopmental impairment. Erythropoietin (Epo) is a haematopoietic cytokine which has been shown to have neuroprotective and neuroregenerative effects on the brain, and which is widely used to treat anaemia in premature infants. Epo has anti-inflammatory, anti-excitotoxic, anti-oxidant and anti-apoptotic effects on neurons and oligodendrocytes and promotes neurogenesis and angiogenesis. One previous retrospective trial indicated that infants treated with Epo scored significantly higher on measures of neurodevelopmental outcome at school age. These neuroprotective effects are thought to arise from a putative reduction in brain injury, but to date the effects of Epo on cerebral microstructure in preterm infants have not been established. The purpose of this study was to investigate the neuroprotective effects on Epo on the development of white matter in preterm infants.

Methods: The patient group consisted of 58 preterm infants (36 male) born between 26 and 31 weeks gestation, of whom 34 were treated with 3 doses of 3000 IU/kg Epo and 24 were treated with an equivalent volume of saline. Epo/placebo treatments were administered intravenously before 3 hours of age after birth, at 12-18 and at 36-42 hours after birth. MR imaging studies were performed at term-equivalent age (37-44 weeks) with a 3T GE HDxt TwinSpeed MRI scanner (GE Healthcare, Milwaukee, WI, USA), using an 8-channel receive-only head coil. All infants were scanned during natural sleep. The structural MRI protocol included axial T2-weighted FSE (TE/TR = 102/5640, resolution 0.4x0.4x2.5 mm3), coronal PD/T2-weighted FSE (TE= 26/128 ms, TR= 6600 ms, resolution 0.7x0.7x1.5 mm3), and axial T1-weighed SPGR images (TE/TR= 2.6/5.7ms, TI= 750 ms, flip angle= 12, resolution= 0.8x0.8x1.4 mm3). Diffusion tensor images were acquired using a pulsed gradient spin echo EPI sequence with 21 non-collinear gradient directions (TE= 77 ms, TR= 9 seconds, field of view = 18 cm, matrix= 128x128, slice thickness= 3 mm, b=1000). Voxelwise statistical analysis of the fractional anisotropy (FA) data was carried out using TBSS. After alignment of the FA maps to the most typical FA map for the group, a mean FA image was created and thinned to create a mean FA skeleton representing the centres of all tracts common to the group. This skeleton was thresholded at a FA level of FA > 0.15, and voxelwise cross-subject statistics were used with randomise (v2.1) to test for differences in FA between infants treated with Epo and placebo using a general linear model, including the gestational age at birth and the corrected gestational age at the time of the scan as covariates. Correction for multiple comparisons was performed by controlling the family wise error (FWE) rate following threshold free cluster enhancement (TFCE).

Results: Preterm infants treated with Epo demonstrated increased FA in the genu and splenium of the corpus callosum, the external capsule, the corona radiata and centrum semiovale, the anterior and posterior limbs of the internal capsule, and the corticospinal tract bilaterally (p<0.01, corrected; figure 1). There were no voxels where FA was significantly higher in preterm infants treated with placebo.

Figure 1. Mean FA skeleton (green) overlaid on the mean FA map in the axial, coronal, and sagittal planes. Regions demonstrating a significantly higher FA in the Epo-treated group are overlaid in red-yellow (p<0.01, corrected).

Discussion: Structural brain abnormalities in preterm infants are typically manifested in a characteristic pattern of injury affecting the cerebral white matter, thalamus, cerebellum, basal ganglia, brainstem, and cerebral cortex, thought to result from an increased vulnerability to ischaemia and inflammation (eg due to infection), and excitotoxicity. The observed increase in FA in infants treated with Epo may therefore indicate protection and repair from brain injury. Neurodevelopmental follow-up data should help to clarify the developmental significance of these findings, and offer insight into the potential utility of Epo as a preventative treatment for the encephalopathy of prematurity.

Conclusion: Early Epo administration improves white matter development in preterm infants assessed by tract based spatial statistics.