

Multiple doses of erythropoietin provide long-term histological & behavioral protection following neonatal stroke

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Background: Recent evidence has shown that exogenous Erythropoietin (Epo) is neuroprotective and may improve functional outcome in rodent models of brain injury. We have previously shown histological and functional protection 2 weeks after focal ischemia-reperfusion with a single dose of Epo, but the long-term response is unclear.

Objective: To clarify the long-term response to single or multiple dose treatment regimens of Epo administered following neonatal stroke.

Design/Methods: Transient focal cerebral ischemia was produced in P10 rats by right middle cerebral artery occlusion (MCAO) for 45 minutes. Injury involving striatum and cortex was verified during occlusion by diffusion-weighted MRI. Either vehicle, single-dose Epo (5 U/g, given immediately after injury), or multiple doses of Epo (1 U/g immediately after injury, 24 hours, and 7 days later) were administered i.p. Experimental groups included vehicle-sham, single-dose Epo (Epo1) sham, multi-dose Epo (Epo3) sham, vehicle-MCAO, Epo1-MCAO, and Epo3-MCAO. For behavioral analysis, sensorimotor performance, visual-spatial learning and memory were assessed at approximately 3 months of age, after which brains were harvested for stereologic volume analysis.

Results: Preserved hemispheric tissue volume (ipsi/contra) in Epo3-MCAO animals (81%) was significantly greater than both vehicle-MCAO (39%) and Epo1-MCAO animals (42%, $p < 0.05$). Epo3-MCAO animals also had a significant improvement in striatal, neocortical, and primary visual cortical volume, with a trend toward increased hippocampal volume, compared to Epo1-MCAO and vehicle-MCAO groups. Epo1-MCAO and vehicle-MCAO animals performed significantly worse than shams in Morris water maze, rotorod, and cylinder rearing tests. Epo3-MCAO animals did not differ from shams for any sensory-motor or spatial memory behavior, except escape latency. There was also a significant correlation between the size of these brain regions and functional performance.

Conclusions: These data suggest that while a single dose of Epo does not confer long-term benefits following neonatal brain injury, 3 doses of Epo preserve brain volume and improve functional outcomes. The mechanisms for these long-term improvements remain to be determined.