Might erythropoietin save the spinal cord in aortic interventions?

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Complex aortic surgery can carry high rates of morbidity, especially the devastating injury of paralysis from spinal cord ischemia. Advances in aortic surgery have allowed more aggressive treatment of previously untreatable disease, including thoracic endografts and open surgical replacement of aortic pathology. Aortic conditions that are associated with high mortality rates from rupture require intervention despite the high risk of paraplegia.

Many adjuncts to surgery have been developed and are currently used to ameliorate spinal cord ischemia by varying methods. Spinal cord perfusion is dependent on the driving pressure (arterial pressure) in relation to the central nervous pressure, and a spinal cord drain to reduce central pressure is often placed and maintained for a few days after the surgical or endovascular intervention. Permissive or active induction of hypertension is used in a similar attempt to maintain blood flow to the spinal cord from collateral sources. Other methods of protection of the spinal cord include hypothermia, preconditioning, and staged reperfusion or “postconditioning,” all which have demonstrated some protection against spinal cord ischemic injury.¹⁻³

However, none of these methods of protection provide a molecular basis or target for protection of the spinal cord. Mares et al⁴ have demonstrated some intriguing information concerning potential molecular mechanisms that when activated by erythropoietin (EPO) provide protection for the spinal cord and a subsequent decrease in paraplegic complications in a murine model. EPO is an interesting cytokine. Its major known action is preventing apoptosis of hematopoietic progenitor cells, which induces increased rates of generation of blood cellular components with the resultant improvement of anemia. However, EPO has been shown to be protective against ischemia of several tissue types, including kidney, liver, skin, and brain. Recent promising effects of EPO in the central nervous system have prompted studies in the treatment of stroke and in

neonatal patients.⁵ These protective effects are due to the presence of additional EPO receptors in nonhematopoietic tissue.

EPO has an additional heterodimer receptor consisting of the EPO receptor and a beta common receptor, with a shared subunit for several different cytokines. This unique receptor complex has been identified in neural tissue and implicated in the protection of ischemic injury by increasing STAT and AKT pathways, which inhibit apoptosis.^{6,7} Spurred by preliminary findings of neural protection in premature infants, current trials for neuroprotection in neonatal cardiac surgery are being conducted.⁸ These trials are exciting; if EPO proves to be efficacious by these pathways, then additional potential therapies for neuronal protection may exist in several areas, including patients undergoing aortic surgery. These studies have prompted the current investigation, and this is an exciting line of inquiry in which patient outcomes might be affected directly with the application of a known treatment modality with few side effects.

EPO treatment for ischemic injury in the central nervous system has great potential, but caution must be exercised before applying a treatment to humans that has proven efficacious in only a small number of animals. Small clinical trials in humans evaluating efficacy for neuroprotection have shown promising results, but large prospective randomized studies failed to demonstrate a benefit of EPO for brain protection and showed unwanted side effects, especially thrombotic complications.⁹ Some studies of EPO in patients undergoing heart surgery have had limited success without increases in complication rates: A meta-analysis including more than 400 patients undergoing heart surgery did not show efficacy in reducing acute kidney injury with the administration of EPO, but subgroup analysis did show potential reduction in the low-risk group and no increase in complication rates.¹⁰ Neuroprotective properties were evaluated in the randomized, double-blind, placebo controlled, proof-of-concept The Erythropoietin NeuroProtective Effect: Assessment in CABG Surgery trial. In this trial, there was a trend in improved neurocognitive outcomes after 2 months.¹¹ Although this was not a definitive trial, it provides evidence that EPO may have some neuroprotective properties that could mitigate some of the adverse outcomes associated with ischemia of the central nervous system, providing additional evidence that supports continued research in this line.

Even if EPO does not eventually provide a clinically significant treatment option for central nervous tissue ischemia, the pathways demonstrated in the murine model by Mares et al⁴ provide a specific line of investigation

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that warrants further inquiry, with possible development of treatment for the prevention of spinal cord ischemia and resultant paraplegia. A new management strategy would be warmly welcomed in a world of aortic surgery that treats life-threatening disorders of the aorta but also carries the burden of the risk of losing the use of the lower extremities.

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