Commentary

Beneficial effects of erythropoietin in preclinical models of shock and organ failure

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See related research by Kao *et al*., http://ccforum.com/content/11/3/R58

Abstract

Erythropoietin protects many organs against the tissue injury and dysfunction caused by ischaemia/reperfusion and excessive inflammation. This editorial comment discusses the effects of erythropoietin in preclinical models of septic shock, endotoxemia, hemorrhagic shock, spinal cord trauma and zymosan-induced multiple organ failure.

Erythropoietin (EPO) is a 34 kDa glycoprotein hormone that controls the proliferation, differentiation, and survival of erythroid progenitor cells through an antiapoptotic mechanism. It has become apparent that EPO protects many organs, including brain, heart, kidney and liver, against the injury caused by ischaemia/reperfusion, hemorrhagic shock and systemic inflammation. In this issue of *Critical Care*, Kao and colleagues [1] report their findings in an established murine model of polymicrobial sepsis.

They found that recombinant human EPO (400 IU/kg) exerts significant beneficial effects when it is given as late as 18 hours after caecal ligation and puncture (CLP). Although EPO had no effect on the (small) decline in blood pressure, the decline in platelet and white blood cell counts, or the rise in lactate, it significantly increased tissue perfusion and reduced tissue hypoxia. Within 18 hours after CLP there was a decline in the number of perfused capillary beds (reduced oxygen delivery); this, in turn, resulted in an impairment in mitochondrial electron transport and hence respiration (measured as increase in mitochondrial NADH fluorescence) in skeletal musle (extensor digitorum longus). Most notably, EPO rapidly (within 10 min) reversed both of these effects of CLP, and hence it increased the number of patent capillaries and increased mitochondrial function. Unfortunately, the authors did not measure any parameters of organ injury and dysfunction, and the model of CLP used did not (within 24 hours) result in any deaths. Thus, it remains to be seen whether the improvement in oxygen delivery or mitochondrial function afforded by EPO also results in a significant improvement in outcome.

The study by Kao and coworkers [1] is of particular importance because EPO protects the brain [2], heart [3], kidney [4] and liver [5] against the tissue injury and dysfunction caused by ischaemia/reperfusion (for review [6,7]). The pathophysiology of the shock associated with trauma/haemorrhage also comprises elements of ischaemia/reperfusion injury (because of hypovolaemia and resuscitation) as well as excessive inflammation. In 2004, we reported that administration of EPO (300 IU/kg intravenously) upon resuscitation reduced the renal dysfunction and liver injury caused by severe haemorrhage and resuscitation in rat [8]. These beneficial effects of EPO were associated with a reduction in tissue (renal) apoptosis secondary to prevention of activation of caspase-3, -8 and -9. Interestingly, EPO also prevents motor neurone apoptosis and associated neurological disability in an experimental model of spinal cord injury [9].

Low doses of EPO (300 IU/kg intravenously) did not affect the organ injury/dysfunction caused by high doses (6 mg/kg) of the Toll-like receptor-4 agonist lipopolysaccharide (LPS) within 6 hours in the rat [8]. However, higher doses of EPO (4,000 IU/kg given 30 min before LPS) attenuated the renal dysfunction (decline in glomerular filtration rate), which occurred at 16 hours after injection of low-dose LPS (2.5 mg/kg intraperitoneally) in mouse [10]. This beneficial effect of EPO in murine endotoxaemia was not due to effects of EPO on either renal blood flow or apoptosis, but it was associated with prevention by EPO of a fall in renal tissue superoxide dismutase activity associated with endotoxaemia.

CLP = caecal ligation and puncture; EPO = erythropoietin; LPS = lipopolysaccharide.

Thus, Mitra and coworkers [10] concluded that the observed beneficial effects of EPO in murine endotoxaemia are secondary to both antioxidant and anti-inflammatory effects of EPO, which have been reported in other models of disease [11]. Thus, the beneficial effects of EPO in rodent models of endotoxaemia may vary with doses of EPO and LPS, as well as species (rat or mouse) used. Interestingly, higher doses of EPO reduce both the systemic inflammation and the organ injury caused by the Toll-like receptor-2 agonist zymosan in mouse [12]. Specifically, treatment of mice with EPO (1,000 IU/kg subcutaneously, 1 and 6 hours after zymosan) attenuated the signs of local (peritoneal exudation) and systemic (lung inflammation), as well as organ (lung, liver and pancreas) injury and dysfunction (kidney) caused by zymosan. Most notably, EPO reduced the high mortality (70%) caused by zymosan over the observation period of 7 days [12].

The reported beneficial effects of EPO in preclinical models of shock, trauma and haemorrhage are exciting, but further studies are warranted to determine the effects of EPO on outcome (organ injury/dysfunction and survival) in models of CLP. Interestingly, in 86 patients admitted to a long-term acute care facility, administration of weekly recombinant human EPO ($n = 42$) resulted in a significant reduction in exposure to allogeneic red blood cell transfusion and higher haemoglobin levels than placebo ($n = 44$) during the initial 42 days of EPO therapy [13]. Although not significant, the mortality rates in patients treated with EPO (12%) were lower than in the patients treated with placebo (23%).

Competing interest

The author is funded by the William Harvey Research Foundation (unrestricted research grant) to study the tissue-protective effects of EPO and has presented a number of invited lectures in this area of research.

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