Erythropoietin use in the critically ill: current evidence

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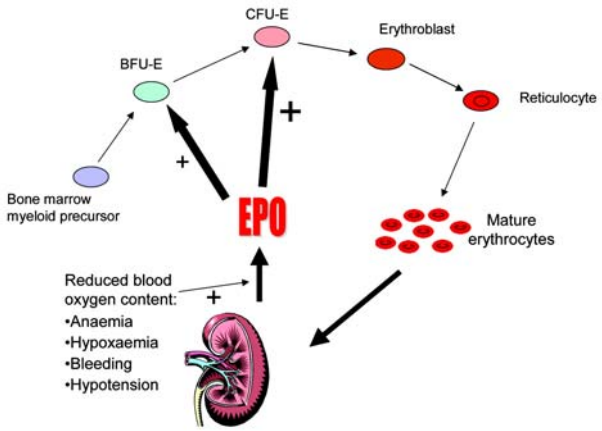
Erythropoietin (EPO) is a haemopoietic glycoprotein consisting of 165 amino acids and four carbohydrate groups. It is a cytokine of the class 1 cytokine superfamily and was first identified as the hormone responsible for mammalian erythropoiesis through its interaction with its specific cellular receptor — the erythropoietin receptor (EPOR). This is a member of the type 1 superfamily of single-transmembrane cytokine receptors.

EPO is synthesised by renal interstitial fibroblasts and, to a lesser extent, by the liver. Plasma levels are regulated by renal oxygen-sensing mechanisms, which respond to stimuli such as hypoxia, hypotension, blood loss and anaemia by increasing EPO production.[1] An increase in red cell mass is promoted both by an increase in the proliferation and differentiation of bone marrow erythroid progenitor cells and by prolongation of erythrocyte survival. The progenitor cells develop in two distinct steps. First, committed erythroid burst-forming units (BFU-E) develop from myeloid stem cells. Then, under the influence of EPO, the BFU-E cells proliferate into erythroid colony-forming units (CFU-E), also referred to as pro-erythroblasts. These cells are highly sensitive to EPO, and develop into erythroblasts and then reticulocytes, which enter the circulation for maturation into red blood cells (Figure 1).

Low levels of EPO are a well-recognised consequence of chronic renal insufficiency and are one of several major factors that contribute to anaemia in patients with long-term renal failure. The administration of exogenous recombinant human-EPO (rH-EPO) to these patients with chronic anaemia is a major treatment advance, although it is worth noting that two recent large trials have demonstrated the potential for harm if high haemoglobin levels (Hb > 120 g/L) are targeted.[2,3]

While the essential contribution of EPO to erythrocyte production has been well established for decades, there has been increasing recognition over the past 10 years that EPO may play an important role in the development, proliferation and survival of non-haematological cells. Much of this relatively recent broader appreciation of EPO's pleiotropic effects stems from the discovery of the erythropoietin receptor on cells in many different tissues, including brain, spinal cord, vessels, muscle, gonads and the eye.[4] Indeed, the brain also produces EPO (of a slightly different structure to that synthesised in the kidney), and it seems likely that this is essential for brain function and development.[5] There is also emerging evidence for EPO having cell protective anti-oxidative, anti-apoptotic and anti-inflammatory effects,

Figure 1. Role of erythropoietin in haemopoiesis



Key: EPO = erythropoietin. BFU-E = erythroid burst-forming units. CFU-E = erythroid colony-forming units.

which may attenuate injury resulting from ischaemia and reperfusion.

Clearly, EPO therefore seems to have several properties that make it potentially beneficial to administer to critically ill patients. Anaemia is almost universal during the course of critical illness, and dysregulated inflammation, tissue malperfusion and oxidative stress have all been identified as important contributing factors to organ injury. A mounting body of evidence indicates that some of these possible benefits may hold true, but not all the promised effects of EPO administration have eventuated, and some patients may even be at risk of harm from unintended side effects.

EPO levels in critical illness

In health, plasma EPO levels remain fairly constant, at levels substantially lower than those of most other comparable hormones.[6] Factors that reduce blood oxygen availability, such as hypoxaemia, hypotension and anaemia, all stimulate renal production of EPO. Some of the inflammatory mediators known to increase during critical illness, such as interleukin-1 (IL-1) and tumour necrosis factor (TNF), can inhibit EPO production and, along with IL-6, can also directly interfere with erythropoiesis.[7] In critically ill patients with acute renal failure, EPO levels tend to track the pattern of the acute phase response to an injurious event:[8] EPO levels remain elevated during the first 48 hours and then fall to levels similar to those in critically ill patients who do not

have acute renal failure (the low–normal range). Interestingly, these levels are not substantially different to those found in many chronically, not critically, ill patients with anaemia. It has been suggested that these findings support the concept that, for treatment of anaemia in the critically ill, pharmacological doses of EPO may be more appropriate in the later rather than early phase of illness.[8] Concerns also exist about the likelihood of other factors interfering with the efficacy of EPO in promoting erythropoiesis in the critically ill. A blunted marrow response to EPO, alterations in iron-handling, nutritional deficiencies and direct myelodepression by inflammatory mediators might be expected to mitigate any potential benefit predicted to occur with EPO therapy in many intensive care patients.

EPO to treat anaemia in critically ill patients

Most patients in the ICU develop at least some degree of anaemia and many receive red cell transfusions.[9,10] Until relatively recently, transfusing these patients was considered to be without substantial risk and universally beneficial, but concerns about safety,[11] and the desire to conserve a scarce resource have increased interest in methods to reduce transfusion requirements. As EPO has an established role in treating the anaemia of chronic renal failure, it is an obvious agent to try in critical illness. Issues are whether EPO can firstly increase haemoglobin levels, secondly decrease transfusion requirements, and finally improve patient outcomes.

A recent meta-analysis[12] identified nine studies of EPO-receptor agonists in critically ill patients, which included a total of 3326 ICU patients. EPO alfa is the only form of EPO studied in the ICU context, and doses ranged between 40 000 units per week to four times this amount. EPO alfa clearly stimulates erythropoiesis in critical illness[13-15] and during the convalescent phase,[16] causing a small elevation of haemoglobin concentrations compared with placebo. However, the observed increases of around 5 g/L attributed to EPO alfa administration in these studies could not be regarded as being of major clinical importance. EPO does protect in terms of independence from transfusion, and slightly reduces the number of transfusions required in the event that blood is administered. Interestingly, these modest transfusion-sparing benefits were not evident in the most recent and largest of the studies evaluated,[15] which was performed in the context of the now commonplace restrictive (Hb < 80 g/L) approach to transfusions. Similarly, delayed administration (after 12.5 days) did not substantially alter haemoglobin concentration or transfusion requirements.[17]

In terms of patient outcomes, EPO administration offers few apparent benefits. Mortality seems little affected, regardless of patient subgroup, dose of EPO alfa administered, or transfusion threshold practice. Non-statistically significant trends to small reductions in mortality are evident for patients assigned to lower doses of EPO and restrictive transfusion practices, and higher mortality is possibly evident with high doses of EPO alfa and liberal transfusion practice. The exception to this apparent lack of impact on mortality may be in trauma patients,[15] with significant reductions in death rates at Days 29 and 140 for patients given EPO.

Adverse events attributed to EPO are of major concern to clinicians, particularly as the most common complications relate to thrombotic events in an already vulnerable patient population. The incidence of deep venous thrombosis seems to be genuinely increased by EPO administration, but pharmacological prophylaxis with heparin may offset this risk.[15] No meaningful differences were found with EPO administration in duration of mechanical ventilation, ICU length of stay, or hospital length of stay in any of the studies reviewed. Assessment of the cost effectiveness of EPO to reduce expensive transfusions and their complications indicate that such an approach cannot be justified.[18]

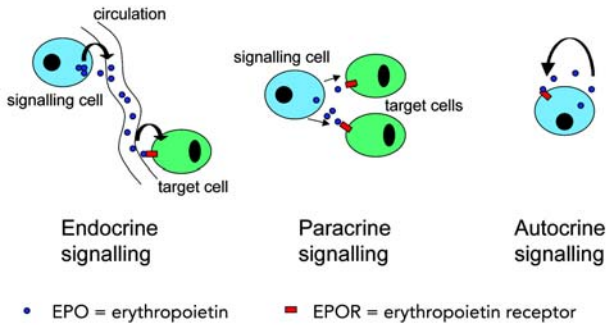
Several questions remain with regard to the failure of EPO administration to improve red cell production in ICU patients in a clinically meaningful way. Most probably, the poor haematological response reflects a host of factors common in the critically ill. These include bone marrow resistance to EPO in critical illness, direct bone marrow suppression by inflammatory mediators, reduced availability of iron stores, depletion of other haematopoietic nutritional reserves, and ongoing red cell loss and premature destruction.

Other roles for EPO in the critically ill

Given the outcomes of studies of EPO use in critically ill patients over the past 10 years, it is hard to argue there is any reason to promote this as a legitimate strategy for treating anaemia in the ICU. EPO provides little increase in haemoglobin concentration, reduces transfusions by a very modest amount, does not alter patient outcomes (except perhaps in trauma), and may have important vascular complications. However, EPO is now recognised to have potentially important effects beyond the kidney–EPO–bone marrow axis, and some of these may be useful in managing critical illness.

The concept of EPO as a hormone is well established and familiar to clinicians. From its production in the kidney, its transport in the circulation and its action on a distant target organ (the bone marrow), EPO has all the classic hallmarks of a hormone. However, newly discovered sites of synthesis and action have expanded understanding with regard to EPO's biological roles and offer

Figure 2. Endocrine, paracrine and autocrine action of erythropoietin



new insights in to the pathophysiology of critical illness and possible therapies. As well as a being conventional hormone, EPO can be rightly considered to have a paracrine role when it is produced by neurological tissue and acts upon adjacent cells. Also, autocrine activity has been demonstrated, where EPO acts on receptors found on the same cell from which it was produced (Figure 2). These latter two systems have been demonstrated in the brain, spinal cord, eye and heart.[19] The erythropoietin receptor is also of increasing interest to oncologists, as it is expressed by many tumours. Interference in this signalling pathway might offer therapeutic options for some forms of malignancy.[20] Substantial research will be required to ascertain the interaction and importance of these three distinct systems.

Several animal models support the concept that EPO is a cytoprotective cytokine. Evidence from animal studies indicates that EPO can reduce ischaemia/reperfusion injury to the intestine,[21] kidney,[22] heart,[23] brain[24] and retina.[25] EPO and the erythropoietin receptor have both been implicated in tissue stress responses. Injured tissues increase expression of the erythropoietin receptor and develop local increases in EPO levels. These changes appear critical to preventing excessive spread of inflammatory and apoptotic tissue damage during exposure to pro-inflammatory cytokines. Evidence from ischaemic pre-conditioning studies suggests that EPO plays an important role in subsequent cellular protection.[26] Animal studies and human clinical evaluations also indicate that EPO administration after an injurious event can be beneficial. This is especially the case for neurological ischaemic injury, where infarct size can be reduced, neuronal recovery enhanced, and functional performance improved.[27] In terms of other clinical studies, there is also evidence of improved functional performance from EPO administration in patients with heart failure,[28] although increased haemoglobin levels could clearly also contribute to such results, making it difficult to draw strong conclusions at present.

If EPO can indeed provide protection from tissue injury caused by ischaemia/reperfusion and inflammatory insults, optimal timing of administration may be important. Interestingly, while early administration is clearly likely to provide the most benefit, even moderately delayed dosing may still offer substantial protection. This may be especially so for injured neurological tissue at high risk of apoptotic changes that progress over many hours.[29] All studies investigating EPO use to treat anaemia in ICU patients have involved drug administration relatively late (at 2 to 10 days), so that such potentially cytoprotective effects may not be achieved. Studies seeking to evaluate non-erythropoietic cytoprotective effect in critically ill ICU patients will need to ensure that adequate tissue levels are achieved at an appropriately early stage to maximise the potential for benefit.

Conclusions

Given the weight of evidence from the clinical studies thus far, treating anaemia in the critically ill with EPO cannot be recommended. A lack of efficacy in terms of increased haemoglobin concentrations and reduced transfusion requirements is matched by a failure to meaningfully affect the need for mechanical ventilation, length of ICU stay, patient survival or health care costs. Of concern is the possibility of an increased incidence of thrombotic complications through EPO therapy. With regard to the non-haematopoietic effects of EPO, more research is needed. In addition to ongoing laboratory and animal studies, human clinical trials, especially in the area of acute myocardial infarction, neurotrauma and stroke, are warranted to establish whether the promising cytoprotective qualities of EPO can improve patient outcomes in the ICU.

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