Erythropoietin for critically ill trauma patients: A missed opportunity?

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Every experiment proves something. If it doesn't prove what you wanted it to prove, it proves something else.–Anonymous

Trauma patients admitted to the intensive care unit (ICU) have a high mortality (10–15%).[1] The development of trauma systems, improved resuscitation strategies, and progress in the care of critically ill patients have significantly improved the outcome of critically ill trauma patients. However, there have been few other successful interventions that have specifically impacted the outcome of critically ill trauma patients.

In 2007, the results of a large multicenter randomized controlled trial of epoetin alpha in critically ill patients were reported, which demonstrated a significant mortality benefit in trauma patients treated with epoetin alpha.[2] In 2008, in this journal, a detailed analysis of the trauma cohort from this trial and an earlier multicenter trial[3] demonstrated that the mortality benefit observed was independent of baseline trauma-specific variables.[4] In the subsequent 8 years, there has been no follow-up of these findings.

In the following commentary, we examine the use of erythropoietin stimulating agents (ESAs) in the critically ill and explore whether further study of ESAs in the critically ill trauma patient is warranted.

Anemia in Trauma and Critical Illness

Anemia is common in critically injured trauma patients, persists through the duration of critical illness, and is associated with worse clinical outcomes.[5,6] The belief that anemia is "bad" has led to the understandable conclusion that correcting this anemia must be "good." This rationale has driven red blood cell (RBC) practice for most almost 50 years.

A major feature of the anemia of critical illness is a failure of circulating erythropoietin concentrations to increase appropriately in response to the reduction in hemoglobin concentration (Fig. 1).[7] This blunted endogenous erythropoietin response has also been documented in trauma patients.[8] These observations suggested that treatment with pharmacologic doses of ESAs might raise the hemoglobin concentration and as a result reduce allogeneic RBC transfusion requirements in critically ill patients.

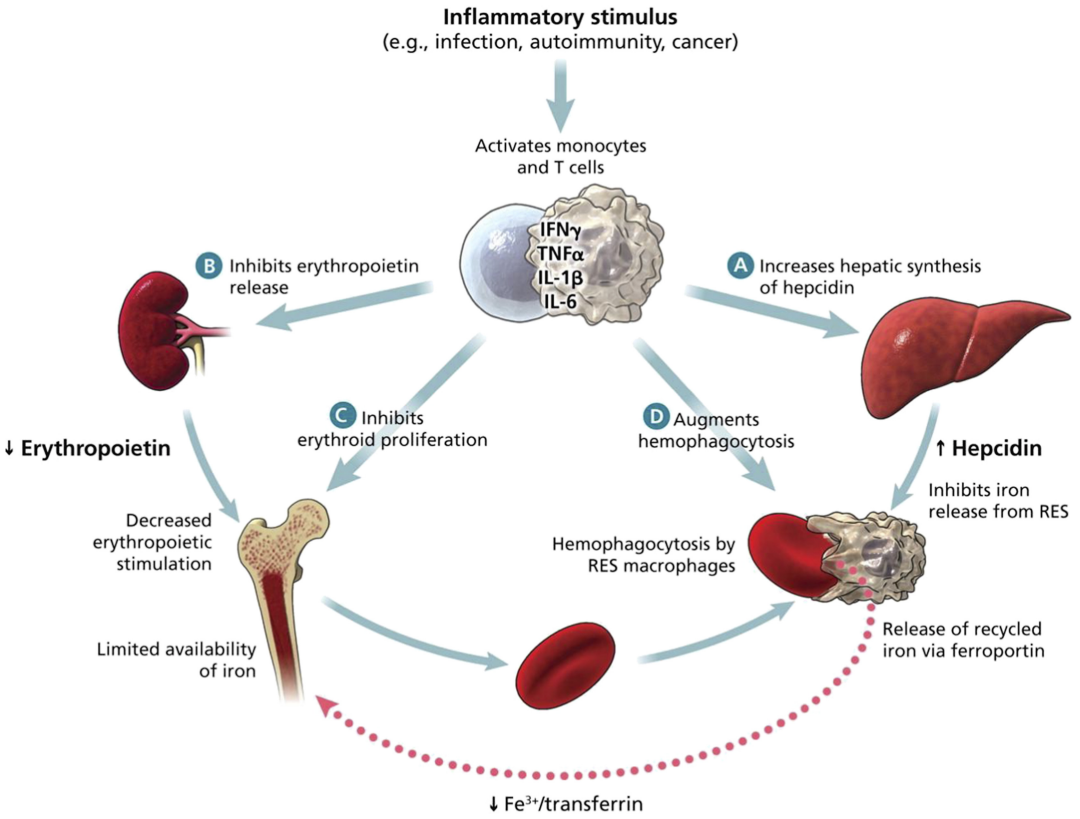

Figure 1. Underlying mechanisms of anemia in trauma. In inflammatory diseases (including trauma, tissue injury, and hemorrhage), cytokines released by activated leukocytes and other cells exert multiple effects that contribute to the reduction in hemoglobin levels and inability to recover from anemia. *A*, Induction of hepcidin synthesis in the liver (especially by interleukin 6 [IL-6] and endotoxin). Hepcidin in turn binds to ferroportin, the pore that allows egress of iron from reticuloendothelial macrophages and from intestinal epithelial cells. Binding of hepcidin leads to internalization and degradation of ferroportin; the corresponding sequestration of iron within the macrophages limits iron availability to erythroid precursors. *B*, Inhibition of erythropoietin release from the kidney (especially by IL-1β and tumour necrosis factor α [TNF-α]). Erythropoietin-stimulated hematopoietic proliferation is in turn reduced. *C*, Direct inhibition of the proliferation of erythroid progenitors (especially by TNF-α, interferon γ, and IL-1β). *D*, Augmentation of erythrophagocytosis by reticuloendothelial macrophages (by TNF-α). RES, reticuloendothelial system. Reprinted with permission.[36]

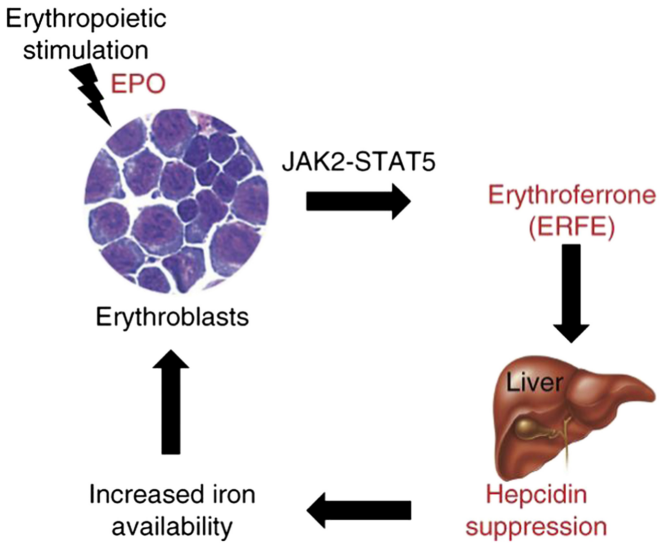

Figure 2. Proposed role of the erythroid factor ERFE. Previous studies suggested that high levels of EPO cause hepcidin suppression indirectly by inducing the secretion of erythroid regulators from the bone marrow, which in turn act on the liver to suppress hepcidin expression and increase iron delivery from dietary absorption and stores. A new hormone and erythroid regulator, ERFE, has been identified, which suppresses the hepatic synthesis of the principal iron-regulatory protein hepcidin, resulting in increased iron uptake. ERFE production by erythroblasts is greatly increased when RBC synthesis is stimulated, such as after bleeding, or in response to anemia. In normal volunteers, erythropoietin administration was sufficient to profoundly lower serum hepcidin levels in less than a day without any significant changes in serum iron concentrations, and its action was presumed to be mediated via ERFE. Reprinted with permission from Macmillan Publishers Ltd.[37]

The rationale is that an increase in endogenous erythropoiesis will result in higher hemoglobin concentration, a more rapid return to a normal hemoglobin concentration, and thus a reduced need for RBC transfusions. A corollary to this is that avoidance of the negative effects of transfused RBCs would improve clinical outcomes.

Our understanding of the pathophysiology of anemia in trauma and critical illness has increased greatly in the last decade. Hepcidin, a 25–amino acid peptide hormone made by hepatocytes, is a key mediator of anemia of inflammation as a regulator of iron metabolism.[9,10] Hepcidin synthesis is up-regulated with inflammation, resulting in reduced iron availability. Hepcidin mediates iron homeostasis by binding to the iron exporter ferroportin, inducing its internalization and degradation, with resultant decreased absorption of iron through the gastrointestinal tract and decreased release from the reticuloendothelial system (Fig. 1). Hepcidin levels rise to extremely high levels after trauma and are positively correlated with injury severity and duration of anemia.[11] Erythropoietin stimulation via ESA treatment results in decreased hepcidin expression.[12] Additional studies document that hepcidin is an important modulator of the acute inflammatory response.[13,14]

Most recently, a new hormone (erythroferrone [ERFE]) has been identified, which mediates hepcidin suppression (Fig. 2). ERFE mediates hepcidin suppression to allow increased iron absorption and mobilization from stores. Interestingly, ERFE is produced by erythroblasts in response to erythropoietin treatment.[15] These experimental findings suggest that ESA treatment, via modulation of both hepcidin and ERFE, may have significant impact on the acute inflammatory response in trauma.

ESA and RBC Transfusion Reduction in Critical Care

The previously mentioned rationale for ESA treatment (to increase endogenous erythropoiesis and reduce RBC transfusion) led to a small randomized pilot study (160 patients) that demonstrated a significant reduction in the number RBC units transfused with epoetin alpha treatment almost two decades ago.[16] This was followed by a much larger multicenter randomized trial (1,302 patients) that confirmed the finding of RBC transfusion reduction.[3] Similarly, a small trial of patients in a long-term acute care facility setting after ICU discharge found RBC transfusion reduction with epoetin alpha treatment.[17] However, a second large multicenter randomized trial (1,460 patients) surprisingly found no RBC transfusion reduction with epoetin alpha treatment, although hemoglobin concentration did rise.[2]

A meta-analysis of nine clinical trials, including the previously mentioned studies that provided more than 80% of the patients, suggested a small reduction in RBC transfusion with ESA therapy.[18] After more than a decade of studies, the inescapable conclusion is that our original hypothesis that treatment with pharmacologic doses of ESAs would reduce allogeneic RBC transfusion requirements in critically ill patients is not supported by the data. There was no reduction in RBC transfusion with epoetin alpha therapy. This is likely related to more restrictive RBC transfusion practices; ESA resistance (common in trauma and critically ill patients) due to inflammatory mediators, which impair erythropoietic cell proliferation and iron availability; and inadequate iron dosing.

ESA and Reduced Mortality in Trauma Patients

While epoetin alpha did not reduce RBC transfusion, an unexpected finding was that mortality in trauma patients was significantly lower with epoetin alpha treatment. The mortality benefit in the trauma subgroup was initially suggested in a post hoc analysis of the initial large clinical trial.[3] The finding was confirmed in a prospective analysis in the most recent trial in which the population was stratified by admission subgroup (trauma, surgery nontrauma, medicine).[2]

Trauma patients treated with epoetin alpha had a significantly reduced mortality at Day 29 (adjusted hazard ratio, 0.36; 95% confidence interval [CI], 0.18–0.74), Day 42 (adjusted hazard ratio, 0.35; 95% CI, 0.18–0.68), and Day140 (adjusted hazard ratio, 0.40; 95% CI, 0.23–0.69). This mortality reduction was independent of baseline trauma-specific variables and was greatest in patients with high Injury Severity Score (ISS) at admission (ISS $\geq$ 25; mortality, 9.4% placebo vs. 5.0% epoetin alpha).[4] In contrast to the trauma patient cohort, mortality was not significantly decreased in either medicine or surgery (nontrauma) patients receiving epoetin alpha. In contrast, functional outcomes in trauma patients receiving epoetin alpha for up to 12 weeks after hospital discharge were not improved.[19]

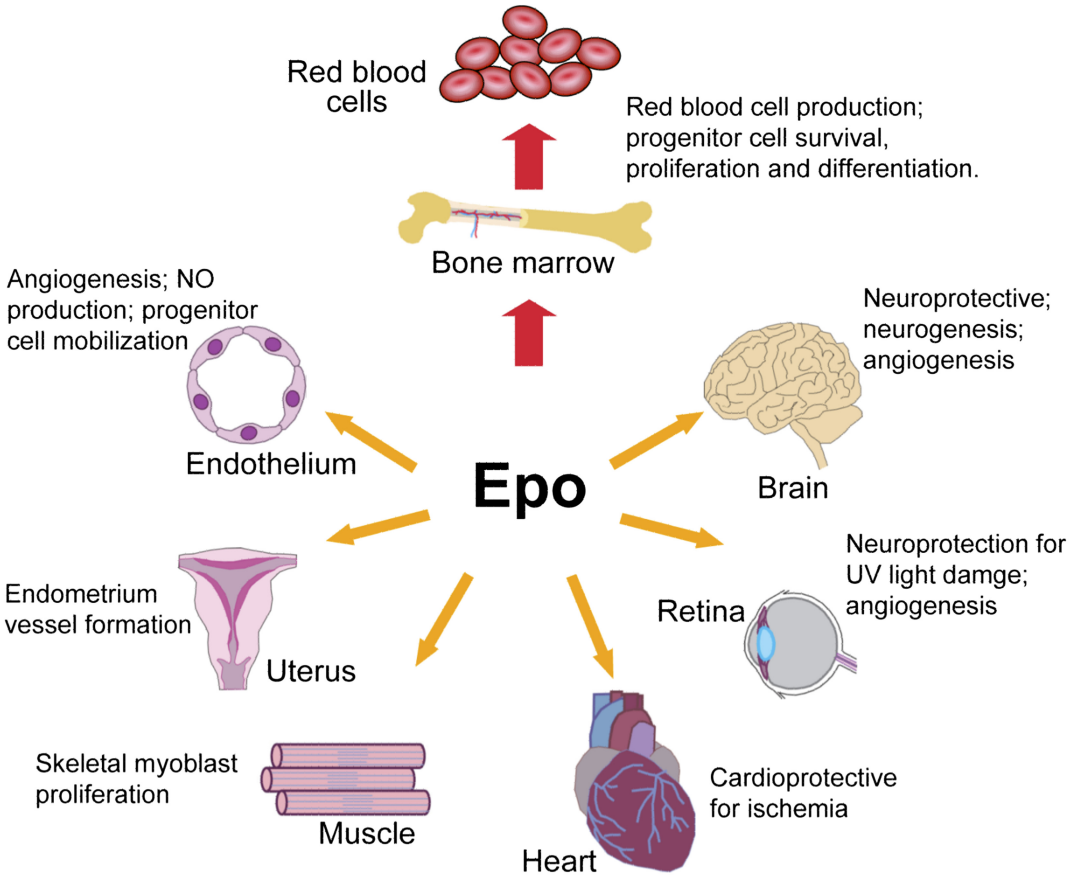

Figure 3. Erythrpoietin (Epo) activity in multiple tissues. Epo acts primarily to regulate erythropoiesis in the bone marrow by stimulating erythroid progenitor cell survival, proliferation, and differentiation to produce mature RBCs. Epo receptor expression on endothelial cells, the endometrium (lining) of the uterus, skeletal muscle myoblasts, the heart, as well as endothelial cells and neural cells in the retina and brain allows EPO to also act as a survival or mitogenic factor on these nonhamatopoietic cells, providing the potential for a response to EPO in multiple tissues. Reproduced with permission from Cambridge University Press.[38]

Can the conclusion that epoetin alpha therapy improves survival in trauma patients be drawn from the available data? Accepting this conclusion depends on the strength of subgroup analysis of the two large multicenter randomized trials.[2,3] Subgroup analysis can present a challenge, and guidelines for determining whether subgroup differences are real have been suggested.[20] These guidelines include the following. (1) Are the differences caused by chance? (2) Are the findings consistent across studies? (3) Are they based on a priori hypothesis? (4) Is there a biologic rationale?

Taken together, the two trials, with a study cohort of 1,433 trauma patients, provide strong evidence in support of a mortality benefit for epoetin alpha in trauma patients.[4] The findings are consistent in direction and magnitude across both studies. In the initial trial, the analysis was not based on an a priori hypothesis but rather was performed as an a priori safety analysis requested by the Data Safety Monitoring Committee.[3] In the second trial, the analysis was based on an a priori hypothesis, and patient randomization was stratified by admitting group.[2] In contrast, the interaction between the stratification group and study group was not significant ($p = 0.16$).[3] Therefore, while the trauma subgroup finding of decreased mortality with ESA treatment is consistent across trials and based on an a priori hypothesis, which increases the likelihood of a real finding, "chance" cannot not be definitively ruled out.

Is there a biologic rationale for the trauma subgroup effect? Our initial hypothesis was that any improvement in clinical outcome would result from transfusion avoidance; however, the mortality reduction observed was independent of transfusion reduction. In view of the absence of RBC transfusion reduction, the mortality effect observed in trauma patients is likely a result of nonhematopoietic actions of erythropoietin and also could be related to modulation of hepcidin expression with resultant impact on the acute inflammatory response.

Why the mortality benefit with epoetin alpha was only observed in trauma patients is unclear. Certainly, trauma patients represent a population very different from other critically patients, with increased acute inflammation related to tissue injury, hemorrhage, and shock.

However, whether some subgroups within the nontrauma critically ill patient cohort may also benefit requires further study.

Nonhematopoietic Actions of Erythropoietin

In addition to the essential role for erythropoietin for mature RBC production, erythropoietin is a pleiotropic hormone with nonhematopoietic biologic effects in many nonhematopoietic

tissues (Fig. 3).[21,22] Erythropoietin is a cytokine with antiapoptotic activity and has been demonstrated in preclinical and small clinical studies to protect cells from hypoxemia/ischemia.[23,24] Multiple tissues express erythropoietin and the erythropoietin receptor in response to stress that mediate local stress responses.[25] There is increasing evidence that erythropoietin and its receptor function as a paracrine/autocrine system to mediate the protection of tissues subjected to metabolic stress.[26]

Results from multiple studies suggest that endogenous erythropoietin signaling contributes to wound healing responses, physiologic and pathologic angiogenesis, and the body's innate response to injury in the brain and heart.[27] These "nonhematopoetic" activities of erythropoietin in protecting cells could be responsible for improved outcomes in critically ill trauma patients.

These effects of erythropoietin are locally mediated through tissue protector receptors and modulate the actions of proinflammatory cytokines. Recent clinical interest has centered on the potential role for ESA in neurologic, myocardial, and renal injury.[28] Administration of erythropoietin just before reperfusion in a pig model of ventricular fibrillation-induced cardiac arrest was associated with higher rates of return of spontaneous circulation and higher 48-hour survival.[29] A small human trial documented that erythropoietin given during CPR significantly increased return of spontaneous circulation as well as 24-hour and hospital survival.[30]

ESA Adverse Events

Epoetin alpha therapy in the critically ill (all patients) was associated with an increase in thrombotic events (hazard ratio, 1.41; 95% CI, 1.06–1.86).[2] This is consistent with trials in non–critically ill populations (cancer and chronic renal failure) where epoetin alpha used to achieve higher target hemoglobin concentrations (i.e., >12 g/dL) has shown an increased risk of thrombotic complications and mortality.[31,32] In a recent meta-analysis of ESA in critically ill patients, while there was no increase in adverse events in general, there was a significant increase in thrombotic vascular events noted.[33]

In the trauma cohort of the 2002 study, no difference in thrombotic events was identified. In the 2007 study, there was a trend to increased thrombotic events in the epoetin alpha trauma cohort (14.5% vs. 12.5%; relative risk, 1.31; 95% CI, 0.93–1.85). However, significant limitations to these study data for venous thromboembolism (VTE) included the following: (1) data were collected as significant adverse events, leading to reporting variability; (2) there were no standardized detection and prevention strategies for VTE; (3) no standardized VTE risk factors were prospectively collected, so comparative analysis for VTE risk was limited; and (4) less than 40% of subjects were receiving some form of VTE prophylaxis on the first study day.

Efforts underway to develop nonhematopoietic, tissue protecting erythropoietin derivatives may make it possible to avoid adverse effects of ESA while using these agents for tissue protection.[23]

Should Trauma Patients in the ICU Receive ESAs?

ESAs should not be used for RBC transfusion reduction based on trial evidence to date. However, the potential for ESAs to increase survival in trauma patients remains an open question. The strength of the subgroup findings across the two largest studies suggest a potential benefit of epoetin alpha treatment for trauma patients admitted to the ICU for more than 48 hours and meeting the other study criteria.

However, while intriguing, any recommendation for routine treatment of trauma patients in the ICU with ESAs awaits further confirmatory study.[34] What is surprising is that in the last 8 years since the publication of the last trial, there have been no additional trials to confirm or refute these findings. Clinical trials have been initiated with far less "pilot" data than are now available for ESA treatment of critically ill trauma patients. Whether this is a result of a lack of interest by the companies producing ESAs or a concern of adverse events given the FDA "black box" warning for ESAs or simply lack of general awareness of the findings or other factors is unknown. Regarding general awareness of the results of clinical trials, the delay for evidence from clinical studies to be incorporated into clinical practice can be considerable. Balas and Boren have estimated that it may take more than 15 years from publication of a "landmark" study for the results to reach a 50% use rate in clinical practice.[35]

We believe that the trauma community is missing a tremendous potential opportunity to improve the outcome of critically ill trauma patient and urge efforts to organize a well-designed definitive clinical trial to evaluate the effect of ESAs in the trauma population. We now recognize that the therapeutic benefits of ESAs can be far beyond the correction of anemia. Newer ESA derivatives that are nonhematopoietic and tissue protecting may ultimately serve as the ideal ESA to improve patient outcomes. Future studies should focus on the nonhematopoietic actions of ESAs as a better understanding of these mechanisms may help to identify why trauma patients benefit and to identify other patient populations that could also potentially benefit.

DISCLOSURE

The authors declare no conflicts of interest.

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