Erythropoietin in the Critically Ill

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Abstract

Introduction: Erythropoietin (EPO) is a recombinant human glycoprotein hormone that stimulates erythropoiesis. There is increasing experience in its use in management of anemia in the critically ill. Methods: This review focuses on clinical, experimental papers regarding erythropoietin usage in the critically ill from the Medline database. Data from our intensive care unit (ICU) were also included. Results: Anemia occurs commonly in the critically ill during ICU stay. Erythropoietin responses are blunt in MODS. EPO is an effective means of increasing haemoglobin and reduces blood transfusion. High doses 300-600U/kg of EPO produce erythropoietic responses within 6 days. For the general critical care patient, studies to date have not shown any increase in adverse events, nor any mortality benefit. Conclusion: Clinical indications include those in whom transfusion is difficult, such as Jehovah’s witnesses, or patients with antibodies. Data in the critically ill support the use of 600U/kg subcutaneously weekly for 4 weeks, with adjuvant therapy of oral iron 300mg/day, vitamin C 100mg/day, folate 5mg/day and possibly vitamin E. We recommend commencing when Hct is less than 30% in patients likely to remain in the ICU beyond one week. Patients should be monitored for hypertension and haemoglobin response. Erythropoietin use is now established as an efficacious, easy to use and safe method of treating anemia in the critically ill.

Introduction

Anemia is a common problem in the critically ill and may have deleterious cardiac as well as oxygen carrying capacity effects. With increasing evidence to suggest benefit in restricting blood transfusion, alternatives are being sought. Erythropoietin (EPO) use appears to be a safe and a promising alternative in the critically ill.

Anaemia in the Critically Ill

In our intensive care unit (ICU), the incidence of patients with a Hct <36% on admission was 75% [1], (Figure 1) and an incidence of 95% by day 3 of ICU admission has been reported [2]. Important causes of anaemia in the critically ill include frequent blood sampling [3-5], invasive procedures, bleeding from the gastrointestinal tract [4,5], surgical blood loss, inappropriately low EPO, and nutritional deficiencies of iron, vitamin B12 and folate [3,8,9]. Management must therefore be multimodal. (See Table 1)

Frequent blood sampling contributes substantially to the fall in hemoglobin (Hb). An average of 41 ml of blood was taken per patient per 24 hours in a survey involving 145 European ICUs [10], and the Hb was found to fall by 5.2 g/L/d over the first 3 days of ICU admission, with a further decrease of 2.9 g/L in septic patients [11].

Physiology of EPO

EPO is produced primarily in the peritubular cells in the cortex of the kidney in response to changes in oxygen delivery. It is regulated by a highly responsive feedback system to maintain a set level of red cell mass. It is unknown why the set level is a particular level in any given animal. Normal red cell production is dependent on basal plasma EPO levels of 0.8-4.0 pM/L.
Table 1. Techniques for managing anemia

<table>
<thead>
<tr>
<th>Technique</th>
<th>Management</th>
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<tbody>
<tr>
<td>Stop the bleeding</td>
<td>Nutritional support</td>
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<tr>
<td>Thrombopoietin</td>
<td>Respiratory support</td>
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<tr>
<td>Erythropoietin</td>
<td>Maintain vascular volume</td>
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<tr>
<td>Iron (enteral or parenteral)</td>
<td>Maximize DO₂, minimize VO₂</td>
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<tr>
<td>Vitamin C</td>
<td>Red cell transfusion</td>
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<tr>
<td>Folic Acid</td>
<td>Blood substitutes</td>
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<tr>
<td>Vitamin B-12</td>
<td>Hyperbaric Oxygen</td>
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DO₂: oxygen delivery, VO₂: oxygen consumption

(5-25 U/L). Isolated in 1977 by Goldwasser in Chicago, EPO gene cloning has since allowed the production of recombinant human erythropoietin (rhEPO).

The EPO gene encodes a protein precursor of 193 amino acids (aa). Cleavage of a 27aa leader sequence yields a mature protein that undergoes glycosylation at 4 sites. Different isoforms of endogenous erythropoietin molecule contain from 4-14 sialic acid residues at each site. Glycosylation is important for altering pharmacokinetics but appears to have no significant biological effects. The C terminal arginine is removed to produce a final form of 165 amino acids. Its tertiary structure is defined by four antiparallel α-helices with adjoining loops. Intact single molecules bind to two adjacent erythropoietin receptors (EPO-Rs) on the membrane of erythroid precursor cells and trigger an intracellular signaling cascade that regulates cell survival, proliferation and differentiation. Alpha, beta and gamma erythropoietin are all produced endogenously with identical aminoacid sequences and activity, their only difference being in the carbohydrate moieties attached. On average, EPO is a 30.4 kDa glycoprotein with 39% of its mass being carbohydrate. Endogenous and rhEPO are currently indistinguishable by assay.

Deficient erythropoiesis occurs when the normal exponential rise in erythropoietin seen in the presence of anemia is lost [13]. In patients with infection or an inflammatory state, erythropoietin secretion, iron delivery and erythroid precursor proliferation are all suppressed by inflammatory cytokines such as tumour necrosis factor-α (TNF), interleukin-1α (IL-1), interleukin-1β, and tumour growth factor-β. Increased oxidative stress can also limit the formation of EPO and inhibit erythroid precursor cells [11]. Endogenous EPO levels of 124 IU/L in septic anemic patients contrast with 845 IU/L in ambulatory anemic patients [13]. Inflammation also induces a shift of iron from the circulation into storage sites, with a reduced amount of...
iron released from the reticuloendothelial macrophages [11]. Finally reduced red cell survival due to phagocyte removal of senescent red cells and those coated with immune complexes or immunoglobulins may contribute [11]. Blunting of the EPO response occurs in critically ill children as well as adults [12,13].

There are approximately 200 to 1000 EPO-Rs on each erythroid progenitor cell, and 20-30% receptor occupancy is sufficient to stimulate erythropoiesis. It is thought that serum EPO must remain above 30 IU/L to stimulate erythropoiesis. Incomplete knowledge of mechanisms of erythropoiesis have led to empiric EPO dosing regimes and adjuvant therapies.

EPO-Rs have been detected in many different cells and tissues, providing evidence for autocrine, paracrine and endocrine functions. Apart from its endocrine action of stimulating maturation of erythroid colony forming units, it may play a role as an antiapoptotic agent associated with enhancement of muscle tone, mucosal status, and gonadal and cognitive function [14].

**Pharmacology of EPO**

There are three forms currently available: EPO alfa, EPO beta and darbepoietin alfa. EPO alfa is a purified glycoprotein hormone produced from mammalian (Chinese hamster ovary) cells encoded with the human erythropoietin gene. Four carbohydrate chains are attached to the protein. It is available as a sterile phosphate buffered solution with 0.03% polysorbate 80 and 0.5% glycine. The intravenous (IV) half life is about 6 hours. Subcutaneous (SC) EPO alfa has a bioavailability of 25%, reaching peak levels after 12-18 hours post dose. The half-life for this route is about 24 hours. Pharmacokinetics are similar for both normal and uremic individuals [15]. EPO alfa is no longer recommended for SC administration in patients with ESRF due to the risk of pure red cell aplasia resulting from antierythropoietin antibodies [16].

EPO Beta is a rhEPO with fewer N acetylneuraminic acid in its carbohydrate portion compared to EPO alfa. The IV route has a half life of 4-12 hours with a volume of distribution between 1-2 times plasma volume. The SC route has an availability of 23-42% with peak concentrations reached 12-28 hours post dose. The terminal half life averages 13-28 hours [17]. No antibodies have as yet been documented.

For both isoforms, intravenous administration follows a monoexponential decay. EPO’s volume of distribution approximates plasma volume, suggesting mainly intravascular distribution. Plasma half life in healthy dogs was 9.0h, and 13.8h in anephric dogs. However in patients with renal impairment or ESRF there was no significant difference in half-lives: 8.5, 8.8, 10.4h respectively in patients with creatinine clearances >80ml/min, 10-50ml/min, <3ml/min) [18]. Perfused dog livers and rats treated with hepatotoxic D-galactosamine demonstrate hepatic removal of EPO. However, nephrectomized, hepatectomized sheep show no difference in plasma clearance or elimination half-life. A possible explanation is receptor mediated endocytosis and inactivation by cell surface peptidases in the bone marrow. However, kinetics appear unchanged in individuals with bone marrow hypoplasia, hyperplasia or ablation [18].

Doses used IV and SC are unchanged despite the decreased bioavailability with SC dosing, as the effect on Hct for identical doses is the same. The SC route is recommended as it follows a more physiological course with a delayed peak concentration and levels persists for 4 days [19].

Darbepoietin alfa has an amino acid sequence that differs from endogenous EPO at 5 positions due to the addition of 2 extra N linked carbohydrate chains. The increased sialic acid containing carbohydrate residues (22 vs 14 with rhEPO) result in a larger molecular weight of 38kDa. In-vitro affinity for the EPO receptor is less than the endogenous EPO, which is compensated by its increased in-vivo potency [20].

IV administration of darbepoietin resulted in a three times longer half life, 2 times greater area under the concentration-time curve, 2-3 times lower clearance, with a similar volume of distribution to that of rhEPO. By SC administration, darbopoeitin has a 2 times longer half life, with a dosing interval that is twice that of other isoforms of rhEPO [21]. Given SC, peak concentrations reach 10% of the IV dose at around 54 hours and levels persist 7 days, with bioavailability around 37%. Patients requiring the highest doses of maintenance rhEPO (15-30000 IU/week) demonstrated a tendency for increased Hb concentrations and dose reductions when switched to IV darbepoietin alfa. The optimal weekly dose was found to be 0.45 ug/kg by the IV and SC routes in dialysis depents patients [20]. Neutralizing antibodies have not been reported.

Side effects are similar for all isoforms of rhEPO and include dose dependant hypertension, or aggravation of existing hypertension in ESRF patients. Hypertensive crises with headaches, confusion, hallucinations...
or cerebral convulsions are rare. These effects are more common by the IV route and may be the result of hemodynamic changes produced by the increase in hematocrit [22].

Thrombocytosis with a slight increase in thromboembolic events, thrombosis at vascular access sites, splenic infarction and clotting in the dialyzer have also been reported [23]. “Flu-like” signs and symptoms and skin reactions of rash, pruritis, urticaria or injection site reactions may occur. Anaphylaxis and anaphylactoid reactions are rare.

Administration results in a fall in iron levels. Concurrent treatment with 200-300 mg Fe/d is recommended for all patients with serum ferritin below 100ug/L or transferring saturation below 20%. Transient increases in potassium and phosphate may occur [22].

Contraindications include: uncontrolled hypertension, hypersensitivity to the constituents, patients at risk of thromboembolism, recent myocardial infarction, acute coronary syndromes or stroke [22].

**Anemia is Detrimental**

Systemic physiological adaptations occur in anaemia to increase oxygen delivery (DO2). These include increases in cardiac output due to tachycardia, increased stroke volume and a decreased systemic vascular resistance, decreased blood viscosity, a shift of the oxygen dissociation curve to the right, erythropoiesis and increases in oxygen extraction from the blood. In critically ill patients, the compensatory mechanisms may be impaired or may increase the demands on the myocardium at a time when the oxygen delivery is decreased and metabolic demands increased.

Anemia, defined as Hct<36% or Hb< 120 g.L-1, is particularly detrimental to those with cardiac disease. There is an increased incidence of postoperative myocardial ischaemia and morbid cardiac events amongst those with a Hct less than 28% [24]. The relative risk of mortality in patients with cardiovascular disease associated with a low Hb level was consistently higher than in patients without cardiovascular disease [25].

In the US medicare hemodialysis database now totaling 74,598 patients, Cox regression analysis revealed increasing mortality with Hct < 36% [26]. This data allowed the reimbursement for EPO usage in end stage renal disease (ESRD) patients with Hct <36%, implying an optimum Hct of 36%. In a large 14 year retrospective cohort of patients who underwent surgery and declined blood transfusion for religious reasons, the adjusted odds ratio for post-operative mortality increased with decreasing preoperative Hb [25]. After adjustment for APACHE II, Charlson comorbidity index and cardiovascular disease, an increased the risk of death was associated with low pre-operative Hb and a Hb decline of more than 40 g.L⁻¹. Similarly, when we plotted Standardized mortality ratios (ie APACHE II adjusted mortalities) for different levels of admission Hct in n=3421 consecutive patients admitted to our ICU, an increase in mortality with lower Hct was also found (Figure 2), down to a Hct of 0.18 [1] However, in the absence of randomized controlled data, it remains possible that anaemia is a marker of disease severity unaccounted for by adjustment, or that treatment options were inadequate for anaemic patients, rather than a cause of mortality per se.

**The Optimal Haematocrit**

In an anesthetized Jehovah’s Witness patient, a critical DO2 of 4.9 ml.kg⁻¹.min⁻¹ was found [27]. Experiences with Jehovah’s Witnesses have suggested that Hb levels of 50 g.L⁻¹ were safe, despite limitations to the data presented [28]. In terminally ill ICU patients, critical DO2 of 3.8 ml.kg⁻¹.min⁻¹ and 4.5 ml.kg⁻¹.min⁻¹ were found in septic and non-septic patients respectively during withdrawal of therapy [29]. Assuming a 70kg patient with a cardiac output of 5 L/min, and full oxygenation, this equates to a Hb of approximately 40 g.L⁻¹.

A Hb of 50g.L⁻¹ in conscious healthy resting humans did not produce any evidence of inadequate systemic DO2, using changes in VO2 and plasma lactate concentration as markers [30]. However, decreased energy levels, subtle increases in reaction time and impaired immediate and delayed memory was found when Hb level decreased below 60g.L⁻¹ [31,32]. These changes were reversible with erythrocyte infusion. In this group, decreasing the DO2 to 7.3 ml O₂.kg⁻¹.min⁻¹, produced no evidence of inadequate systemic oxygenation. A critical DO2 was not detected [33].

If one argues that the only significant physiological function of red cells is the delivery of oxygen, then optimizing oxygen delivery (DO2) is useful only if it is a limiting factor in oxygen consumption (VO2). Whilst drug or altitude induced erythrocytemia improves performance in competitive athletes [34], due
to extreme VO$_2$ requirements, it has not been shown in the critically ill, that VO$_2$ is limited by DO$_2$, nor that DO$_2$ is limited by Hct. In a number of randomized controlled trials (RCTs) in ICU patients, transfusion had no effect on VO$_2$ in patients with cardiac and septic shock [35], in ARDS patients [36] or in mechanically ventilated septic patients [37]. The plateau in VO$_2$ seen in VO$_2$-DO$_2$ studies do not support any benefit from increasing DO$_2$ (or Hct) above the critical DO$_2$ level.

Consequently, a case may be made that the safe lower limit of Hb is also the optimum Hb, and that from total body VO$_2$ considerations, this appears to be approximately 50g/L. However, the above studies may have been confounded by the use of blood transfusions in the manipulation of patient Hct. The optimal Hct using different methods such as EPO may be different. Further, different tissues and disease states may also have different critical requirements of DO$_2$.

In observational study of patients with acute myocardial infarction, transfusions were associated with a reduction in mortality for patients with a haematocrit of 33% or less. Conversely, subgroup analysis of the Transfusion Requirements in Critical Care Trial found that in patients with confirmed ischemic heart disease, severe peripheral vascular disease or severe comorbid cardiac disease there was no significant (p=0.3) decrease in overall survival with restrictive transfusion practices [39].

A linear relationship between Hct and cerebral DO$_2$ with maximal DO$_2$ occurring at 40% to 45% has been reported [40]. A separate study using PET scans and O$_2$ inhalation found that despite the increased cerebral blood flow with hemodilution, cerebral DO$_2$ decreased, with the optimal Hct being a normal Hct [41]. This suggests that optimal cerebral DO$_2$ is achieved with a Hct 40-45%.

Supranormal oxygen delivery with a specific recommendation of a Hct of 33% has been shown to significantly reduce mortality in surgical ICU patients [42]. Other RCTs [43,44] confirm this result (Table 2) in this patient population. This evidence suggesting a benefit to increasing oxygen delivery in surgical patients who undergo surgery does not appear to improve outcomes in the general ICU population [45]. It is also possible that the benefit may be related to the timing of initiating resuscitation, rather than the specific components of the oxygen delivery regime such as transfusion.

In ESRD patients given EPO, there were major improvements in myocardial function, skeletal muscle strength, exercise capacity, quality of life, cognitive

Figure 2. Relationship between Standardized Mortality Ratio and admission Hct

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brain function and angina. Regression of left ventricular hypertrophy occurred at Hct 33% to 36%, but complete normalization did not occur [46-48]. The Hct considered optimal may have been too low, or irreversible damage already done. Consequently, a number of trials have attempted normalization of Hct in ESRD patients [46]. In the largest trial to report, the Normal Hct Cardiac Trial (US), the trial was discontinued due to excess mortality in the ‘high’ (i.e. normal) Hct group [47]. However, mortality rates decreased with increasing Hct in both groups with a 30% decrease in risk of death for each 10% increase in Hct [48], placing much doubt on the conclusion. However, a more recent uncontrolled non-randomized study raising Hb levels resulted in improvement in left ventricular hypertrophy and associated mortality. It remains uncertain if a Hct which is normal for a healthy individual may be harmful in a patient.

Red cell transfusion is detrimental

The lack of effect of RBC transfusion may be related not only to the dose but also the product. Traditionally, Hct has been manipulated by the use of blood transfusions. Up to 20-50% of ICU patients receive 5 units of blood during their ICU stay [10,50,51], and half of the transfusions are for no identifiable indication or for a ‘low’ Hct alone [52].

In 1717 patients admitted over 2 years the rate of nosocomial infection was significantly higher in the group that received transfusion compared with those who did not. (15.4% vs 2.9%, p<0.05) Each unit of blood transfused was associated with an increased risk of nosocomial infection by a factor of 1.5 [53]. Transfusion was associated with increased length of ICU and hospital stay and higher mortality rates despite controlling for age, sex and probability of survival. Transfusions undoubtedly entail a risk of adverse events, while there is little data of sufficient power comparing clinical and cost outcomes using different methods of attaining any particular Hct.

EPO use in The Critically Ill

Experience with EPO usage in the critically ill patient is increasing. (See Table 2). In a prospective, double blinded, randomized controlled study of 40 acutely burned patients, the EPO treated group had no statistically significant differences in Hb, Hct, or transfusion requirements after 30 days. They received IV 300U/kg daily for 5 days followed by 150U/kg on alternate days for 23 days [54]. Another early trial randomized 19 ICU patients with MODS following surgery or major trauma to either 600U/kg of IV EPO 3 times a week for 3 weeks, or placebo. Erythrocytes increased significantly after 3 weeks in the EPO group compared with placebo. (mean ± SEM. 4%±0.9% vs 1.9%±0.5%) There was a statistically significant difference in erythropoietin levels at the first week. 2 of 7 in the EPO group compared with 6 of 10 in the placebo group required blood transfusions [55].

For patients with congestive heart failure and anaemia (Hb<120 g.L⁻¹), a randomized trial studied the effects of EPO and intravenous iron. There were increases in Hb and left ventricular ejection fraction with a decreased decline in glomerular filtration rate. Mean hospitalizations decreased 91.1%, and there was a decreased dose requirement for furosemide [56].

In a larger RCT, 160 critically ill patients received SC rhEPO 300 U·kg⁻¹ for 5 days, then every other day till ICU discharge for a total of 6 weeks, or placebo. All patients received oral or parenteral iron supplements. EPO was effective in raising Hct and 45% compared with 55% of placebo patients received at least 1 unit of blood. Total units transfused was significantly reduced in the EPO group. (166 v 305 p<0.002) [57] No increase in mortality or adverse reactions occurred (Table 3). Exclusion criteria including active bleeding, neutropenia, thrombocytopenia, unmanaged hypertension, inotrope requirement, liver failure, or seizures.

The efficacy of rhEPO was further confirmed in a prospective, open, randomized trial of 36 critically ill patients with a Hb of <11.2g/dL. Patients received either folic acid 1mg/d for 14 days (control group), folic acid with IV iron 20mg/d (iron group) or folic acid, IV iron and SC rhEPO 300U/kg every 2 days for 5 doses (rhEPO group) [58]. Patients were transfused if Hb reached 89 g/L. There was a statistically significant increase in erythropoietin and in erythrocytes after 6 days in the rhEPO group compared with baseline and the other 2 groups. Reticulocyte counts reached a maximum on day 13 (189±97x10⁹/L from a baseline 56±33x10⁹/L) [58] Blood transfusion requirements were not statistically significantly different, though the study was underpowered. Although there was no difference in adverse events, there was no group in which EPO was prescribed without IV iron, so that detrimental effects arising from IV iron could not be assessed [58].
A large multicentre randomized controlled trial supports the use of erythropoietin in reducing allogeneic blood transfusion in critically ill patients. 1302 patients admitted to the ICU for longer than 3 days were randomized to weekly injections of erythropoietin 40000U (n=650) to a maximum of 4 doses or placebo (n=652); all patients received iron and were followed for 28 days. There was a significant reduction in exposure to any allogeneic blood by about 10% in enrolled patients. (60.4% placebo vs 50.5% with...
rhEPO) [59] Patients receiving rhEPO had a median reduction of 1 unit of blood transfusion and a 0.38g/dl increase in Hb compared with placebo. Total blood units transfused decreased by 19%. Mortality (111 in the rhEPO group compared with 120 in the placebo group), morbidity, length of stay, number of ventilator days or readmission to the ICU were not significantly different [59].

Whilst this study confirmed the efficacy of erythropoietin, no major clinical benefit was demonstrated, which conflicts with the results of multiple studies confirming the adverse effects of transfusions. Further, a transfusion trigger of 85 g/L was used in this study, and it has been suggested the same reduction in transfusion requirements could have been achieved, with an improvement in outcome, by using a lower transfusion trigger [60]. (see Optimum Hct above). Consequently, until a study with sufficient power can document reductions in morbidity or mortality with EPO, the cost of EPO becomes a major issue. The Hong Kong blood bank estimates the cost of 1 unit of leukodepleted RBC unit at around US$160 and American estimates are around US$400 [59]. This compares with our cost of US$442 for a 40000U dose of rhEPO.

**Erythropoietin Administration: Practical Issues**

Specific guidelines for the use of erythropoietin do not currently exist. Well accepted indications in intensive care include patients who refuse blood transfusion, (Jehovah’s Witness) and patients with antibodies who are difficult to cross match. For the general critical care patient, there is no study with sufficiently high power currently available to suggest any benefit other than to reduce the number of blood transfusions required. For those who desire to avoid this, the following conclusions could be drawn:

1. Haemoglobin falls in the critically ill during ICU stay. EPO administration should anticipate this fall.
2. Erythropoietin responses are blunted in MODS and larger doses are required.
3. High doses 300-600 U/kg produce erythropoietic response seen within 6 days.
4. Restrictive transfusion strategies are not harmful and possibly beneficial in patients without severe cardiovascular or cerebral compromise.

Although Corwin [59] commenced EPO when Hct fell below 38% in any patient likely to remain in the ICU beyond 1 week, this ‘EPO trigger level’ can be safely lowered if the transfusion trigger level is also lowered, say to 70 g/L. Assuming the rate of decline in Hct reported by Vincent et al. [10,11] and an erythropoietic response to EPO within 6 days, EPO may be prescribed at a Hct of 30% without greatly increasing the incidence of Hb<70 g/L. This prevents overshoot hyperviscosity and related EPO side-effects from EPO, and is a more rational use of both EPO and transfusion.

In the critical care setting, rhEPO 300U/kg daily for 14 days or 600 U/kg weekly for 4 weeks are used, compared to the usual dosage of 80-120U/kg 3 times weekly in patients with ESRF. The studies in Table 2 all demonstrated rapid stimulation of erythropoiesis with high doses of rhEPO in ICU patients. Such doses (40000IU weekly) have also been shown to be effective at reducing the need for blood transfusions in patients undergoing major orthopedic surgery [61], radical prostatectomy [62], colorectal surgery [63] and chemotherapy [64]. EPO dose-response relationships appear to be similar in patients regardless of age or gender. A dose of 600 U.kg⁻¹ weekly is as efficacious as a 300 U.kg⁻¹ daily dose [61].

**EPO Adjuvant Therapies**

**Iron**

IV iron supplementation has been demonstrated to increase by five-fold the erythropoietic response to anemia resulting from acute blood loss [65], while serum ferritin and transferrin saturation levels decreased by up to 50% during rhEPO therapy [66]. Each 6g of new Hb requires 30-40mg iron daily, liberated from serum ferritin. EPO administration results in a “functional iron deficiency” such that increased erythron iron requirement exceeds the available iron, even in the presence of adequate storage iron [67]. Consequently, supplemental iron is recommended for all patients receiving rhEPO.

The data is conflicting as to whether IV iron supplementation increases the erythropoietic response more than oral iron supplementation [68]. These studies were conducted in relatively healthy patients with adequate oral intake. Oral iron is likely to be inadequate supplementation during rhEPO therapy in the critically ill. Conversely, concerns regarding intravenous iron include the development of iron overload, life threaten-
ing anaphylaxis to dextran, and its potential prooxidant and bacteri-nutritic effect. Hydroxyl radicals and lipid alkoxyl radicals formed by the Fenton reaction can trigger iron induced lipid peroxidation [69]. These effects may however be attenuated with adjuvant vitamin E [70]. The risk and benefits regarding different routes of iron supplementation in the critically ill have not been well addressed.

**Vitamin C**

Ascorbic acid is a water soluble reducing agent that potentiates the mobilization of iron from inert tissue stores and facilitates the incorporation of iron into protoporphyrin. In a prospective RCT of 36 patients with iron overload on hemodialyses, the addition of 500mg/week of vit C increased Hct, decreased ferritin and reduced the total weekly dose requirement for EPO [71]. Vitamin C 100mg/day supplementation allows mobilization of iron stores and improves EPO efficacy.

**Vit E**

There is some data to suggest adjuvant vitamin E therapy alleviates oxidative stress, (Decreased GSSG/GSH to carboxyhemoglobin levels) and increased Hb and Hct levels earlier than rhEPO alone, in hemodialysis patients. In addition vitamin E has a sparing effect on the EPO dosage requirement in HD patients [72].

**Folate**

Folate is a water soluble vitamin with a daily requirement of 50-100ug/d that is essential for DNA synthesis. Folate supplementation had no effect on EPO treated ESRF patients without folate deficiency [73]. However, 1-5mg folate/day is often prescribed because of its lack of toxicity. Deficiency is more commonly encountered in the malnourished, alcohol abusers and should be considered in those with macrocytosis. In vit B12 depleted individuals, high dose folate may cause severe neurological changes such as subacute combined degeneration of the spinal cord, and B12 status should be assessed.

**Alternatives to transfusion**

Various methods of treating anaemia are shown in Table 1. Minimizing bleeding and iatrogenic blood loss is an essential step in the prevention of anaemia. Nutritional support, hematinics and minimizing VO₂ are all important. Alternative methods to improve tissue oxygenation include the use of blood substitutes, such as cell-free haemoglobin, perfluorocarbon emulsions and liposome-encapsulated Hb (Table 3). These other modalities in managing the patient with anemia do not preclude the use of EPO. Unfortunately, diaspirin cross-linked Hb as an adjunct to standard therapy was associated with higher mortality in a randomized controlled trial involving 112 trauma patients [74]. A Phase III trial of perflubron emulsions in cardiac surgery was suspended in 2001 due to adverse neurological outcomes [75]. Hyperbaric oxygen has been shown to sustain the life of pigs which have been completely exsanguinated and replaced with a volume expander, for 4 days, without measurable effects after months of follow-up [76]. Logistical difficulties relegate hyperbaric oxygen to use as a last resort in the management of patients for whom refusal of transfusion is nonnegotiable.

**Conclusion**

Erythropoietin use is now established as an efficacious, easy to use and safe method of treating anemia in the critically ill. Clinical indications may include those in whom transfusion is difficult such as Jehovah’s witnesses, in the field or patients with antibodies. Whilst we know blood transfusions can be significantly reduced, no trials have yet demonstrated a survival benefit with EPO. However, with an increasingly limited supply and the costs of reducing potential infectivity of blood, pharmacoeconomic analysis may increasingly favor the use of EPO. And, as in the case of preoperative autologous blood transfusion, patients may be prepared to bear the burden of increased costs when options are presented.

Data in the critically ill support the use of 600U/kg subcutaneously weekly for 4 weeks, with adjuvant therapy of oral iron 300mg/day, vitamin C 100mg/day, folate 5mg/day and possibly vitamin E. We recommend commencing when Hct is less than 30% in patients likely to remain in the ICU beyond one week. Patients should be monitored for hypertension and haemoglobin response. It is likely erythropoietin’s role in our anemia armament is here to stay.
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