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Recommended Citation
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Review

Anemia and blood transfusion in the critically ill patient: role of erythropoietin

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Published online: 14 June 2004
This article is online at http://ccforum.com/content/8/S2/S42
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Critical Care 2004, **8(Suppl 2):**S42-S44 (DOI 10.1186/cc2411)

Abstract

Critically ill patients receive an extraordinarily large number of blood transfusions. Between 40% and 50% of all patients admitted to intensive care units receive at least 1 red blood cell (RBC) unit during their stay, and the average is close to 5 RBC units. RBC transfusion is not risk free. There is little evidence that 'routine' transfusion of stored allogeneic RBCs is beneficial to critically ill patients. The efficacy of perioperative recombinant human erythropoietin (rHuEPO) has been demonstrated in a variety of elective surgical settings. Similarly, in critically ill patients with multiple organ failure, rHuEPO therapy will also stimulate erythropoiesis. In a randomized, placebo-controlled trial, therapy with rHuEPO resulted in a significant reduction in RBC transfusions. Despite receiving fewer RBC transfusions, patients in the rHuEPO group had a significantly greater increase in hematocrit. Strategies to increase the production of RBCs are complementary to other approaches to reduce blood loss in the intensive care unit, and they decrease the transfusion threshold in the management of all critically ill patients.

Keywords anemia, blood transfusion, critical illness, erythropoietin

Anemia is common in critically ill patients and appears early during their intensive care unit (ICU) course. By day 3 after ICU admission, almost 95% of patients are anemic [1–3]. The anemia in these critically ill patients persists throughout their ICU and hospital stay, with or without red blood cell (RBC) transfusion [3].

Historically, the anemia observed in the critically ill resulted in a high number of RBC transfusions. Studies conducted a decade ago [4] revealed that 50% of all patients admitted to the ICU are transfused during their stay. In addition, 85% of patients with a prolonged ICU stay (>1 week) received transfusions [5]. On average, these latter patients were transfused 9.5 RBC units during their ICU stay. These transfusions are not restricted to the early ICU course; rather, patients are transfused at a rate of 2–3 units per week.

An observational study of 4892 patients admitted to ICUs in the USA throughout 2000 and 2001 [3] found that almost 50% of patients are still transfused. The results also showed that initial RBC transfusion tends to occur early in the ICU stay, with ongoing RBC transfusions throughout the ICU stay. The mean pretransfusion hemoglobin observed (i.e. the 'transfusion trigger') was 8.6 ± 1.7 g/dl – a value that is comparable to that described in earlier reports [4,5]. Interestingly, RBC transfusions were not restricted to the ICU; 13% of patients received on average almost 3 units after ICU discharge.

A similar observational study of transfusion practice in ICUs was performed across Western Europe [6]. Data were collected for a maximum of 28 days on 3534 patients admitted to the ICU during a 2-week period in late 1999. Of these patients 37% received a mean of 4.8 RBC units while in the ICU and 12.7% of patients were transfused during the post-ICU period, for an overall transfusion rate of 42% during the 28-day study period. The mean pretransfusion hemoglobin level was 8.4 g/dl.

 EPO = erythropoietin; ICU = intensive care unit; RBC = red blood cell; rHuEPO = recombinant human erythropoietin.

The similarity in results between these two large observational trials is striking. These studies suggest that transfusion practice in response to the anemia of critical illness has changed little over this period. This is particularly surprising, given the scrutiny to which transfusion practice has been subjected over the past decade. In a prospective randomized study of critically ill patients, Hebert and colleagues [7] demonstrated that maintaining hemoglobin levels in the 7–9 g/dl range is at least equivalent, and in some patients (Acute Physiology and Chronic Health Evaluation II score ≤ 20 or age < 55 years) superior, to maintaining hemoglobin levels greater than 10 g/dl with RBC transfusion. Of note, both observational studies [3,6] found that RBC transfusion was independently associated with worse clinical outcomes.

These observational studies [3,6], as well as the studies conducted by Hebert and coworkers [7,8] and others [9], have raised questions regarding the validity of the historic assumption that RBC transfusion was beneficial for all critically ill patients with anemia. Recent recommendations have advocated that empirical automatic transfusion thresholds be abandoned in favor of a practice of RBC transfusion only for defined physiologic need [10,11]. However, the suggestion for a more conservative approach to RBC transfusion does not yet appear to have resulted in any major alteration in practice patterns.

Phlebotomy is an important factor contributing to anemia and the need for blood transfusions in the critically ill patient. Smoller and Kruskall [12] found that almost half of their ICU patients receiving blood transfusions were phlebotomized more than the equivalent of 1 unit of blood. The ICU patients described in that study were on average phlebotomized 65 ml/day. Phlebotomy blood losses in this range are consistent with other reports of critically ill patients over the past 2 decades, and are often associated with the development of anemia [5,13,14].

It is now clear, however, that the view of anemia in the critically ill as simply the result of excessive phlebotomy by 'medical vampires' is not completely accurate [15]. RBC production in critically ill patients is not normal, and decreased levels of RBC production are also involved in the development and maintenance of the anemia observed in the critically ill.

More than 90% of ICU patients have low serum iron, total iron binding capacity, and iron/total iron binding capacity ratio, but have a normal or, more usually, an elevated serum ferritin level [2,16]. Similarly, low iron parameters and elevated ferritin levels are observed in patients with multiple organ dysfunction [17]. At a time when the iron studies are abnormal, serum erythropoietin (EPO) levels are only mildly elevated, with little evidence of reticulocyte response to endogenous EPO [2]. Rogiers and coworkers [18] compared EPO levels in critically ill patients with those in patients with iron-deficiency anemia. Although EPO levels were somewhat elevated compared with those in adults without anemia, they were significantly lower when compared with patients with iron-deficiency anemia, despite similar levels of hematocrit. A comparably blunted EPO response to physiologic stimuli also has been reported in critically ill children [19].

This blunted EPO response observed in the critically ill appears to result from inhibition of the EPO gene by inflammatory mediators [20,21]. It has also been shown that these same inflammatory cytokines directly inhibit RBC production by the bone marrow and may produce the distinct abnormalities of iron metabolism [22,23].

Anemia of critical illness is therefore a distinct clinical entity, characterized by blunted EPO production and abnormalities in iron metabolism similar to what is commonly referred to as the anemia of chronic disease. As such, the bone marrow in many of these patients may respond to administration of exogenous EPO, despite their critical illness. This may represent a therapeutic option for the treatment of the anemia of critical illness.

In patients with multiple organ failure, recombinant human erythropoietin (rHuEPO) therapy (600 units/kg) was shown to stimulate erythropoiesis [17]. In a small, randomized, placebo-controlled trial of 160 patients [1], therapy with rHuEPO resulted in an almost 50% reduction in RBC transfusions as compared with placebo. In patients with hematocrit below 38% on ICU day 3, rHuEPO was given at a dose of 300 units/kg daily for 5 days, followed by every other day until ICU discharge. Despite receiving fewer RBC transfusions, patients in the rHuEPO group had a significantly greater increase in hematocrit.

The efficacy of rHuEPO demonstrated in the small trial was the basis for a recently completed randomized controlled trial of 1302 patients [24]. In this later trial, rHuEPO was given weekly at a dose of 40 000 units. All patients received three weekly doses, and patients who remained in the ICU on study day 21 received a fourth dose. Treatment with rHuEPO resulted in a 10% reduction in the number of patients receiving any RBC transfusion (60.4% with placebo versus 50.5% with rHuEPO, $P < 0.0004$; odds ratio 0.67, 95% confidence interval 0.54–0.83) and a 20% reduction in the total number of RBC units transfused (1963 units with placebo versus 1590 units with rHuEPO, $P < 0.001$). The reduction in the total number of RBC units transfused was more modest than in the prior trial [1]. This may be a result of shorter follow up (28 days versus 42 days), different dosing of rHuEPO (weekly versus daily followed by every other day), or changes in transfusion practice. Similar to the initial study, the increase in hemoglobin from baseline to final was greater in the rHuEPO group. Clinical outcomes were similar in the rHuEPO and placebo groups.

The effects of critical illness persist well after discharge from the ICU. Therefore, the 'chronically' critically ill constitute a

large and important population of patients. In a small, randomized, controlled trial of 86 patients admitted to a long-term acute care facility [25], a weekly rHuEPO dose of 40 000 units for up to 12 weeks was shown to decrease the exposure to allogeneic blood. There was a reduction in the total units of RBCs transfused in the rHuEPO group (113 units with placebo versus 73 units with rHuEPO). In addition, patients receiving rHuEPO were also less likely to be transfused (61% with placebo versus 31% with rHuEPO, $P < 0.006$; odds ratio 0.28, 95% confidence interval 0.12–0.69). The increase in hemoglobin from baseline to final was greater in the rHuEPO group. Mortality (29.5% with placebo versus 19% with rHuEPO) and adverse clinical events were not significantly different.

Taken together, these studies [1,24,25] demonstrate that rHuEPO therapy in both 'acute' and 'chronic' critically ill patients will result in a decrease in RBC transfusion and an increase in hemoglobin level. This is consistent with the hypothesis that the critically ill patient has an anemia that is similar to anemia of chronic disease and is characterized in part by a relative EPO deficiency [26].

Does a reduction in RBC transfusions with rHuEPO therapy lead to better clinical outcomes? The studies in critically ill patients have not demonstrated differences in clinical outcome associated with reduction in RBC transfusion. Two of the studies [1,25] were small and not designed to detect these differences. However, even the larger trial [24] did not have the power to identify small, but potentially meaningful, differences in clinical outcomes. Further study is needed to determine whether there are clinical outcome benefits in critically ill patients admitted to either the ICU and/or long-term acute care facilities associated with a reduction in the exposure to RBC transfusion with rHuEPO administration.

Competing interests

Dr Corwin has received research support from Ortho Biotech Products, L.P. and has served as a consultant for Ortho Biotech Products, L.P. and Biopure.

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