Erythropoietin in the critically ill: what is the evidence?

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Introduction

In patients with chronic kidney disease receiving regular treatment with recombinant erythropoietins (rHuEPO or epoetins), infection and inflammation may lead to erythropoietin resistance and loss of efficacy. During episodes of acute illness there is variability in practice regarding whether erythropoietin therapy is temporarily halted, maintained unchanged or intensified. Recently, the potential of erythropoietin therapy to increase red cell production in critically ill patients per se has received considerable attention. Experience in this field has interesting implications for the management of chronic anaemia in other clinical settings.

Red blood cell transfusions in critical care

The discussion of the role of erythropoietin in the critically ill cannot be separated from the issues surrounding blood transfusion today. Red blood cell (RBC) transfusion, an integral part of clinical practice for most of the last century, has long been looked upon as relatively ‘risk free’ and with obvious clinical benefits [1]. A dramatic change in thinking occurred in the early 1980s, when concerns about transfusion-related infections, particularly those caused by hepatitis C and the human immunodeficiency virus (HIV), prompted a re-evaluation of the risks of allogeneic blood transfusion. While advances in transfusion medicine have greatly decreased the risk of viral transmission during blood transfusion, other concerns now drive the debate over transfusion practice and have led to a re-examination of the approach to RBC transfusion in the critically ill.

Critically ill patients typically receive multiple RBC transfusions during the acute course of their disease [2–5]. Recent data from both the United States and Western Europe demonstrate that between 35 and 50% of all patients admitted to ICUs today receive on average almost five RBC units during their ICU stay [6,7]. However, the view of RBC transfusion as ‘risk free’ is no longer tenable. In addition to the well described transfusion complications, studies have raised the issue of immunosuppression related to allogeneic blood transfusion [1,7–11], as well as concerns regarding the age of RBCs transfused [12,13]. There is some thought that leukoreduction of transfused RBCs will decrease or eliminate the problem of immunosuppression, although this remains controversial. Adding to the controversy about risk/benefit ratio for RBC transfusion are recent data showing that an aggressive RBC transfusion strategy may decrease the likelihood of survival in selected sub-populations of critically ill adults [14]. Accordingly, limiting exposure to allogeneic RBC transfusions would be advantageous in the critically ill population.

Characteristics of anaemia in critical illness

Production of RBCs by the bone marrow is impaired in critically ill patients and this phenomenon contributes to both the development and, more importantly, the persistence of anaemia. Critically ill patients are anaemic early in their ICU course and haemoglobin levels fall during the ICU stay [5–7]. The anaemia associated with critical illness is probably fundamentally similar to the anaemia of chronic inflammatory disease [15]. In addition to direct inhibitory effects of pro-inflammatory cytokines on red cell production and impaired iron availability a major feature of the anaemia of critical illness is a failure of circulating erythropoietin concentrations to increase appropriately in response to the reduction in haemoglobin levels [5,16–20]. These observations have suggested that treatment with pharmacological doses of
epoetin might decrease exposure to allogeneic blood and raise the haemoglobin level in critically ill patients. The rationale for epoetin therapy is that increased erythropoiesis will result in higher haemoglobin levels, a more rapid return to normal haemoglobin levels, and thus a reduced need for RBC transfusions.

Study results

In patients with multiple organ failure, rHuEPO therapy (600 U/kg) has been shown to stimulate erythropoiesis [21]. In a small randomized placebo-controlled trial (160 patients), the administration of rHuEPO resulted in an almost 50% reduction in RBC transfusions as compared to placebo [22]. Erythropoietin was given at a dose of 300 U/kg daily for 5 days followed by every other day dosing until ICU discharge. Despite receiving fewer RBC transfusions, patients in the rHuEPO group had a significantly greater increase in haematocrit.

The efficacy of rHuEPO demonstrated in the small trial was the basis for a randomized controlled trial of 1302 patients [23]. In this later trial, rHuEPO was given weekly at a dose of 40 000 U. 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% placebo vs 50.5% rHuEPO, P < 0.0004; odds ratio 0.67, 95% CI, 0.54, 0.83) and a 20% reduction in the total number of RBC units transfused (1963 U placebo vs 1590 U rHuEPO, P < 0.001). Similar to the initial study, the increase in haemoglobin 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. While considerable data are available regarding RBC transfusion practice in the ICU, few data are available on transfusion practice in critically ill patients after they leave the ICU. There are, however, some suggestions that at least some of these more ‘chronic’ patients have ongoing transfusion requirements. In patients followed for 30 days after ICU admission, 13% received RBC transfusions after leaving the ICU [6,7]. These patients on average were transfused 3 RBC units after they left the ICU and 40% of the patients were only transfused after they left the ICU [7].

In a small randomized controlled trial (86 patients) of patients admitted to a long-term acute care facility, a weekly dose of 40 000 U for up to 12 weeks was shown to decrease the exposure to allogeneic blood [24]. There was a reduction in the total units of RBCs transfused in the rHuEPO group (113 U placebo vs 73 U rHuEPO). In addition, patients receiving rHuEPO were also less likely to be transfused (61% placebo vs 31% rHuEPO, P < 0.006; odds ratio 0.28, 95% CI, 0.12, 0.69). Increase in haemoglobin from baseline to final was greater in the rHuEPO group. Mortality (19% rHuEPO, 29.5% placebo) and adverse clinical events were not significantly different.

Taken together, these studies [22–24] demonstrate that epoetin therapy in both ‘acute’ and ‘chronic’ critically ill patients results in a decrease in RBC transfusion and a rise in haemoglobin level. This supports the hypothesis that the critically ill patient has anaemia consistent with anaemia of chronic disease which is characterized in part by a relative erythropoietin deficiency [5,15–18]. The dose of rHuEPO at 40 000 U weekly is significantly higher than generally used in patients with chronic kidney disease; however it is consistent with other clinical indications [25,26].

Potential risks and benefits

In the above mentioned trials there was no increase in the number of adverse clinical events reported with rHuEPO therapy. In particular there was no increased risk for thromboembolic complications and no effect on blood pressure was noted. However, the power of these studies may have been too low to identify less common adverse events. Recently, the occurrence of pure red-cell aplasia associated with the presence of anti-erythropoietin antibodies was reported in a small number of chronic renal failure patients treated with rHuEPO administered subcutaneously [27]. This complication, which has mainly occurred in association with the use of the preparation of Epogen used outside the USA, was not observed in these trials, which were conducted in the USA and in which treatment duration and follow-up were relatively short. Meanwhile, factors related to the upsurge of this complication appear to have been controlled.

The comparatively high doses of epoetins required to stimulate erythropoiesis in the critically ill also have the potential to induce extra-erythropoietic effects. Accumulating data indicate that erythropoietin can confer tissue protection under conditions of acute organ injury, including stroke, myocardial infarction and acute renal failure [28–31]. Yet the clinical relevance of such effects remains to be determined. Overall, in view of issues that have been raised regarding the safety and efficacy of RBC transfusions [14] and the potential benefits of epoetin, the important question is whether a reduction in RBC transfusions with rHuEPO therapy leads to better clinical outcomes. The studies in critically ill patients have not demonstrated clinical outcome differences associated with RBC transfusion reduction. Two of the studies were small and not designed to detect these differences [22,24]. However, even the larger trial [23] did not have the power to identify small, but potentially meaningful, differences in clinical outcomes. Further study is necessary 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 the reduction in the exposure to RBC transfusion with epoetin administration.

Conclusions

The results of recent trials in critically ill patients indicate that inhibition of red cell production and erythropoietin resistance in the presence of infection, inflammation and even multiorgan failure can be overcome by using high, pharmacological doses of epoetin. Further refinement of dosing schedules will be required to optimize this therapeutic approach and the issue of iron availability deserves additional consideration. While it is clear that erythropoietin therapy can reduce RBC transfusions, no clinical benefits have as yet been associated with this transfusion reduction. Key in developing guidelines for epoetin use in the critically ill is the selection of those patients most likely to benefit from therapy, namely the ‘long term’ critically ill patient, i.e. with a greater than 1 week length of stay. These patients represent 25–30% of critically ill patients [3,6,7] and are also more likely to require prolonged care. Starting erythropoietin therapy in these patients and continuing this therapy, albeit at higher doses, in renal patients who are hospitalized for acute complications appears to mainly come down to a cost issue and the value placed on transfusion reduction. The cost–benefit relationship still remains to be formally analysed and could change markedly in the future with a decline in cost for epoetins, further increase in the costs of blood transfusions, and a better understanding of the risks and efficacy of RBC transfusion and erythropoietin therapy, respectively [32,33].

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References

Is a major psychiatric illness a contraindication to chronic dialysis?

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The use of an artificial kidney was first commenced in the mid 1940s for the treatment of acute renal failure. Only from the early 1960s were patients with end-stage renal disease (ESRD) accepted for chronic haemodialysis therapy. Initially, those accepted for chronic dialysis were, in general, in excellent medical condition (i.e. without any co-morbidities) apart from their renal failure. They, thus, tended to be young with no evidence of systemic disease. The advent of the external shunt followed by the native arterio-venous fistula in the late 1960s established haemodialysis as a feasible long-term maintenance therapy. However, financial considerations, lack of professional personnel and primitive technology resulted in limited availability of chronic dialysis. One of the major contraindications for acceptance to dialysis was age. In the early 1970s, the average age of dialysis patients was 30–35 years. Over the next three decades, the limitations of acceptance onto a chronic dialysis programme were gradually dissipated. This was mainly due to an increased number of trained dialysis practitioners (both physicians and nurses) and improved technology. As a result, the dialysis patient population underwent a considerable change. In 1999, 47% of the patients entering the Medicare ESRD programme were aged >65 and 23.4% were >75 years [1]. The mean age of dialysis patients in our unit is 66–67 years. Co-morbidity is widespread consisting of multiorgan involvement by diabetes mellitus, generalized atherosclerosis, congestive heart failure, systemic disease and even malignancy (either ongoing or in remission).

The treatment of chronic illness, particularly when it demands dietary and/or fluid restrictions, requires a high degree of patient co-operation, discipline, insight and, last but not least, a strong family support. Without these essentials, the chance of long-term survival is vastly diminished. Depression has been documented as the most frequently encountered psychological problem in (ESRD) patients and has been correlated with both morbidity and mortality in these patients [2]. Undoubtedly, ESRD and/or dialysis eventually lead to physical and at times mental incapacitance [3]. Dialytic therapy represents a unique situation whereby life is maintained artificially but is severely restricted and unsatisfying coupled to an ever-imminent fear of immediate death and a feeling of total dependency on the dialysis machine. Patients are often frustrated, humiliated and angry. The anger is not infrequently vented out at the dialysis staff expressed as multiple complaints and/or verbal confrontations. Of note, as the average age of dialysis patients increases, a greater percentage of these patients are retired pensioners. They are, therefore, relatively less concerned with financial problems, family commitments or the need...