Neuroanesthesia and Intensive Care

Best evidence in critical care medicine

The use of recombinant human erythropoietin to reduce red cell transfusions in critically ill patients

Article appraised

Corwin HL, Gettinger A, Pearl RG, et al.; EPO Critical Care Trials Group. Efficacy of recombinant human erythropoietin in critically ill patients: a randomized controlled trial. JAMA 2002; 288: 2827–35.

Structured abstract

Clinical issue: Allogeneic red blood cell (RBC) transfusions are common in critical care practice. Can recombinant human erythropoietin (rHuEPO) administration reduce the need of RBC transfusions and hence the associated risks?

Methodology (internal validity): Prospective randomized multicentre clinical trial.

Computer generated randomization stratified by site.

Six hundred and fifty patients were randomized to rHuEPO and 652 patients to placebo.

Allocation concealment was by randomization at the data coordinator centre.

Double-blind placebo controlled trial by using similar syringes.

Cointerventions were similar in both groups.

Demographic and baseline characteristics were similar. Outcome assessor awareness of group allocation was not clear.

About 3% of patients were lost to follow-up.

All patients were included in the final analysis using the intention-to-treat principle.

Intervention and outcomes (results): Weekly *sc* injection of rHuEPO (40,000 units) or placebo was started on intensive care unit (ICU) day three for a total of three or four doses.

All outcomes were assessed at the end of the 28th day from the first dose.

Primary efficacy outcomes: Patients receiving rHuEPO were less likely to undergo allogeneic RBC transfusions (60.4% placebo *vs* 50.5% rHuEPO; $P < 0.001$); number needed to treat was 10 and the OR 0.67 (95% confidence interval [CI], 0.54–0.83).

Secondary efficacy outcomes: 1) There was a 19% reduction in the total units of RBCs transfused in the rHuEPO group (1,963 units for placebo *vs* 1,590 units for rHuEPO).

2) The increase in hemoglobin from baseline to study end was greater in the rHuEPO group (mean [SD], 1.32 [2] g·dL⁻¹ *vs* 0.94 [1.9] g·dL⁻¹; $P < 0.001$).

3) There was a reduction in RBC units transfused per day alive in the rHuEPO group (ratio of transfusion rates, 0.81; 95% CI, 0.79–0.83; $P = 0.04$).

4) Mortality was not different between groups (14% in rHuEPO *vs* 15% in placebo; $P = .61$).

5) Adverse clinical events were not significantly different.

Applicability (external validity): Inclusion criteria: hematocrit less than 38% in adult patients on their third day of ICU admission if they were expected to have at least four days ICU stay.

Exclusion criteria: renal failure on dialysis, uncontrolled hypertension, seizures, acute burns, acute coronary syndrome and acute gastrointestinal bleed. The included patients represented about one third of most ICU patients.

The study could not detect clinically important outcomes (mortality and morbidity) likely because of inadequate power. Lack of any obvious adverse events could be due to short follow-up.

In spite of the high dollar cost of rHuEPO, consideration of other factors like blood availability, transfusion complications and long ICU stay costs should be kept in mind.

Conclusion: The administration of 40,000 units of rHuEPO per week in long stay critically ill patients reduces allogeneic RBC transfusion and increases hemoglobin concentration. However, no effects on mortality or morbidities could be found in this study.

Commentary by Osama Almuslim and David Leasa

Insufficient global tissue perfusion is considered to be a trigger for the multiple organ dysfunction syndrome and, subsequently, death.¹ This concept has been a major incentive to adopt a practice of liberal allogeneic blood transfusion in critically ill patients. Conversely, the TRICC trial proved that a more conservative transfusion strategy should be the standard of care in most of these patients.² An additional large prospective observational study (the ABC study) also showed that allogeneic red blood cell (RBC) transfusions were associated with increased morbidity and mortality in critically ill patients.³ In contrast, one large retrospective observational study indicated that elderly patients with an acute coronary syndrome had a survival advantage with a more liberal blood transfusion approach.⁴

The key issue is that allogeneic RBC transfusions should not be thought of as a physiologic replacement of low endogenous hemoglobin. Although it seems logical that a low hemoglobin concentration is detrimental in seriously ill patients, the current evidence does not support using allogeneic RBC transfusions to mitigate this problem. Besides, allogeneic blood transfusions have potential risks like transmitting infective agents and causing adverse immunological reactions. Other transfusion hazards are related to the age of the stored blood and the presence of white blood cells (WBCs), both of which have been linked to immunomodulatory effects. Various studies showed that a transfusion of more than 14-day-old blood could increase the infection rate and mortality.^{5,6} This post-transfusion immunomodulation may be the consequence of old RBCs causing tissue ischemia in addition to immunosuppression by WBC bioactive cytokines.

The management of anemia in critically ill patients needs a paradigm shift. Interestingly, the ancient theme of using endogenous body substances to restore disturbed homeostasis is now proving itself of interest through scientific methodology. Recombinant erythropoietin (EPO) is one example. Wide acceptance of this strategy to reduce the need for allogeneic blood transfusions will continue to face obstacles related to cost, delayed onset of action, current lack of evidence of benefits on morbidity and mortality and unknown long term safety, specially with regard to pure red cell aplasia. Perhaps a more comprehensive approach for long stay intensive care unit patients should include measures to minimize iatrogenic blood loss,³ conservative transfusion guidelines² and therapeutic approaches to stimulate the bone marrow. Currently, transfusion medicine is calling for the TRICC II: such a trial should address the effects of leukoreduction, limiting RBC storage to 14 days and the use of recombinant EPO.

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References

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