Research

Erythropoietin use in critically ill patients: forest and trees

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Published at www.cmaj.ca on Sept. 5, 2007.

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In this issue, Zarychanski and colleagues present a meta-analysis of randomized controlled trials that evaluates the use of erythropoietin in critically ill patients.[1] The primary purpose of this commentary is not to critique their analysis but, rather, to present an overview of the potential role of erythropoietin in critically ill patients. My perspective, and potential bias, is of someone who has had a major involvement in 4 of the included studies, which enrolled more than 90% of the patients included in the meta-analysis by Zarychanski and colleagues.

Anemia is very common among patients who are critically ill. Almost 95% of patients admitted to an intensive care unit have a hemoglobin concentration that is below normal by day 3 of admission.[2] Anemia typically persists throughout their stays in the intensive care unit, and as a consequence these patients receive a large number of red blood cell transfusions.[3,4] The anemia associated with critical illness is fundamentally similar to the anemia of chronic inflammatory disease.[5] A major feature of anemia in critical illness is the failure of circulating erythropoietin concentrations to increase appropriately in response to a reduction in the patient's hemoglobin concentration. These observations have suggested that administering pharmacological doses of erythropoietin will increase the hemoglobin concentration in critically ill patients through stimulation of erythropoiesis and thus decrease their need for allogeneic red blood cell transfusions. A corollary to this is the hope that by avoiding the potentially negative effects of blood transfusions clinical outcomes would improve.

The above rationale for erythropoietin therapy led to a small randomized pilot study with 160 critically ill patients, which showed a reduction in red blood cell transfusions among patients in the erythropoietin treatment group.[6] A much larger randomized controlled trial ($n = 1302$) later confirmed these findings.[7] A post-hoc analysis of this latter trial suggested differences in mortality in subgroups (trauma patients, medicine nontrauma patients and surgery nontrauma patients) with erythropoietin treatment. These studies led to a third randomized trial ($n = 1460$) in which the primary outcome was again transfusion reduction. However, because of the previously observed subgroup differences, the three subgroups were prospectively identified and randomization was stratified on these groups. This study confirmed a mortality benefit among trauma patients receiving erythropoietin.[8] Surprisingly, although there was an increase in hemoglobin concentrations, there was no transfusion reduction found in the erythropoietin group. This suggests that the mortality benefit was independent of transfusion effect. Importantly, there was a significant increase in thrombotic events observed in the erythropoietin treatment group that had not been observed in the earlier studies.

Meta-analysis is clearly a useful technique for combining results from multiple primary studies. However, in this case, was a meta-analysis necessary? There have now been 2 large randomized controlled trials that were similarly designed.[7,8] These 2 studies enrolled almost 85% of the patients in the meta-analysis by Zarychanski and colleagues.[7,8] Combining these 2 studies with others that used different erythropoietin dosing strategies, different patient populations and different clinical situations does not add to the understanding of the role of erythropoietin in critically ill patients. For example, the study by Silver and colleagues[9] included only long-term acute care patients (after transfer from an intensive care unit) who received a much longer duration of erythropoietin therapy (up to 12 doses compared with 3 or 4 doses in the other 2 studies); the study by Still and colleagues[10] included only burn patients, who were excluded in our randomized controlled trials[6–8]; our pilot study[6] used an erythropoietin dosing strategy that resulted in patients receiving a dose double that used in our more recent studies; and erythropoietin dosing strategies were quite varied in the other studies included in the meta-analysis. In the studies for which sample size was calculated,[6–9] sample size was based on transfusion reduction outcomes, not on clinical outcomes. Including all of these additional underpowered studies in a single analysis does not clarify the role of erythropoietin in patients who are critically ill. This issue is particularly important because the timing and the dose, as well as the population studied, may affect the risk–benefit ratio for erythropoietin therapy. The questions of

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DOI:10.1503/cmaj.071150

efficacy and safety can be more clearly answered by a close examination of the 2 large randomized controlled trials that had a similar design.[7,8]

The meta-analysis by Zarychanski and colleagues suggests an overall reduction in the proportion of patients who received transfusions in the erythropoietin group. However, given current transfusion practices, there appears to be no reduction in red blood cell transfusions with erythropoietin treatment. The reduction in the proportion of patients transfused and the total number of units transfused that was observed in the earlier randomized controlled trial[7] was not observed in the most recent trial.[8] The difference in the results between these studies is probably because of significant changes in transfusion practice over the intervening years. Zarychanski and colleagues suggest that some of the studies were consistent with either a restrictive (hemoglobin concentration $\leq$ 80 g/L) or a liberal (hemoglobin concentration $\geq$ 90 g/L) transfusion strategy. In this context, the use of the word "strategy" implies that there was a prospective plan to transfuse patients according to specific criteria, which was clearly not the case. Regardless, it is clear that transfusion practice in general has changed. There was a significant increase in hemoglobin concentration observed with erythropoietin therapy, which demonstrates that erythropoietin had the expected hematopoietic effect, despite the absence of transfusion reduction.

Erythropoietin appears to decrease mortality among trauma patients admitted to the intensive care unit for more than 48 hours. This was suggested in a post-hoc analysis in our prior study[7] and was confirmed in a prospective analysis in our most recent study.[8] Questions often arise as to whether subgroup differences are in fact real. Guidelines have been suggested to help interpret subgroup analyses.[10] These guidelines suggest asking the following questions: Are the comparisons made within studies? Were the subgroups prospectively identified? Was the number of hypotheses tested small? Is the magnitude of the effect large? Is the effect statistically significant? Is the effect consistent across studies? And is the effect biologically plausible? In our most recent study,[8] our analysis of trauma patients is consistent with what would be considered an appropriate subgroup analysis, including biologic plausibility. Taken together, our 2 studies, which included a total of 2762 critically ill patients and 1433 trauma patients, provide strong evidence in support of a mortality benefit for erythropoietin use in trauma patients.[7,8] On the other hand, mortality was not significantly decreased among either medicine nontrauma patients or surgery nontrauma patients who received erythropoietin. Whether some subgroups within the medicine or surgery nontrauma population may benefit from erythropoietin therapy requires further study.

The absence of a reduction in transfusions among patients who received erythropoietin suggests that the observed mortality benefit is a result of nonhematopoietic actions of erythropoietin. Erythropoietin and its receptor are expressed by multiple tissues in response to stress and mediate local stress responses.[11] Erythropoietin is a cytokine with antiapoptotic activity, and it has been demonstrated in preclinical and small clinical studies to protect cells from hypoxemia and ischemia. These nonhematopoetic, cell-protection activities could be responsible for the observed improvement in outcomes among critically ill patients. Further studies will be necessary to establish the mechanisms responsible for erythropoietin's effects. However, in some respects, there is a greater understanding of the nonhematopoietic actions of erythropoietin than there is of the mechanisms that underlie the adverse effects attributed to red blood cell transfusions.

Are there adverse events associated with erythropoietin therapy? Among critically ill patients, erythropoietin use appears to be associated with increased thrombotic events. This is consistent with the results of recent trials involving noncritically ill patients with either cancer or chronic renal failure. In these studies, erythropoietin, when used to achieve higher target hemoglobin concentrations (i.e., > 120 g/L), was shown to increase the risk of thrombotic complications and death.[12–15] A post-hoc analysis performed as part of our most recent trial suggested that this risk can be mitigated by the use of prophylactic anticoagulation therapy.[8] In this study, there was greater awareness of the potential for thrombotic complications, which in part may have led to the differences observed in thrombotic events between the study groups compared with what was reported in the earlier studies. However, as Zarychanski and colleagues point out, more systematic surveillance is necessary in future trials.

What is the role of erythropoietin in patients who are critically ill? To answer this question, Zarychanski and colleagues attempt to create a forest from the trees of the individual trials. However, most of this forest is made up of 2 giant redwoods. The data needed to begin to answer the question are available in the 2 large randomized controlled trials.[7,8] Certainly, the need for an additional trial in a trauma population, as suggested by Zarychanski and colleagues, is important. However, whether erythropoietin should be used in trauma patients before a confirmatory trial is performed and whether investigators have enough equipoise to randomly allocate trauma patients in a third confirmatory trial are important questions. Given the strength of the findings from the subgroup analyses in the 2 randomized controlled trials,[7,8] at this time erythropoietin should be considered for trauma patients who are admitted to an intensive care unit for more than 48 hours and who meet other study criteria (Box 1). On the other

Box 1: Suggestions for the use of erythropoietin in critically ill patients

- Should be considered in trauma patients who are admitted to the intensive care unit for more than 48 hours and who meet the inclusion and exclusion criteria detailed in the latest erythropoietin randomized controlled trial.[8]
- Should not be administered to medicine nontrauma patients or surgery nontrauma patients unless they have an approved indication for erythropoietin.
- Prophylactic anticoagulation should be considered for critically ill patients who receive erythropoietin.

hand, the available data do not support the use of erythropoietin in medicine or surgery nontrauma patients admitted to an intensive care unit, unless they have an approved indication for erythropoietin use. Treating these nontrauma patients with erythropoietin would expose them to potential risks with no identifiable benefits in the form of a reduction in transfusions (assuming conservative practice) or mortality. Prophylactic heparin should also be considered if erythropoietin is given. Future studies should focus on understanding how the nonhematopoietic activities of erythropoietin are beneficial for critically ill patients. A better understanding of these mechanisms may help to identify other populations that could benefit from this therapy as well as identify the optimal timing and dose of erythropoietin therapy.

Competing interests: Howard Corwin has served as a paid consultant and has received research support from Johnson & Johnson Pharmaceutical Research & Development and from OrthoBiotech.

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