

Perioperative Anemia and Blood Transfusions in Patients with Cancer

When the Problem, the Solution, and Their Combination Are Each Associated with Poor Outcomes

Juan P. Cata, M.D.

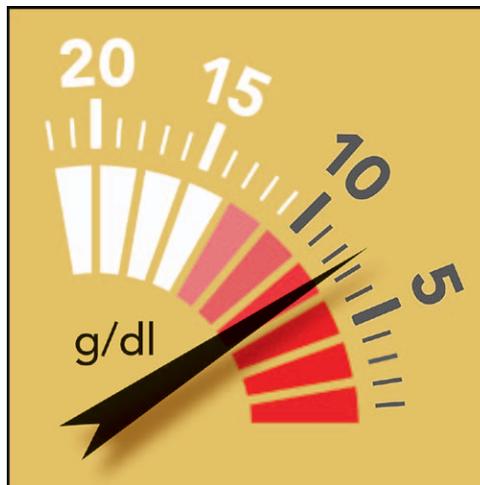


This article has been selected for the ANESTHESIOLOGY CME Program. Learning objectives and disclosure and ordering information can be found in the CME section at the front of this issue.

IN this month's issue of ANESTHESIOLOGY, de Almeida *et al.*¹ elegantly investigated postoperative administration of packed erythrocytes in patients who were admitted to the surgical intensive care unit after abdominal cancer surgery. The study was a controlled, parallel-group, double-blind superiority trial in which patients were randomized to receive blood transfusions using restrictive (hemoglobin <7 g/dl) or liberal (hemoglobin <9 g/dl) criteria. The authors found that patients randomized to the liberal strategy had a lower absolute risk of the 30-day primary composite endpoint that was a composite of all-cause mortality, cardiovascular complications, acute respiratory distress syndrome, acute kidney injury requiring renal replacement therapy, septic shock, or reoperation. Patients assigned to the liberal transfusion strategy also had a lower 60-day mortality.

The prevalence of anemia in patients with cancer ranges from 30 to 90%.² Perioperative anemia in this population is multifactorial and can be the result of the cancer *per se*, its treatment, or chronic kidney disease. Preoperative anemia in patients with cancer usually is the result of blood loss due to advanced cancer or bone marrow suppression secondary to inflammation or myelotoxicity. In contrast, intraoperative and postoperative anemia results from surgical blood loss or administration of fluids (dilutional).

Recently, Loor *et al.*³ developed the concept of “three evils” with respect to anemia and transfusion to explain the association of each and the combination of both with poor



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outcomes after cardiac surgery. This concept can also be applied in patients with cancer; however, patients with cancer are exposed to different risk than cardiac patients and the overall surgical population. Treating moderate-to-severe perioperative anemia (“first evil”) should be considered in patients with cancer for two reasons. First, anemia *per se* can increase the risk of cancer recurrence. Low hemoglobin concentrations can render cancer cells more aggressive through several mechanisms, including tumoral hypoxia and inducing the release of interleukin-6.⁴ Second, patients with cancer appear to tolerate anemia less than the general population. The hemoglobin concentration that is associated with an increase in early postoperative morbidity and mortality in cancer surgery patients appears to be about 8 g/dl. The odds of death increase 2.5-fold for every 1-g decrease in postoperative hemoglobin concentrations below 8 g/dl.⁵ And the mortality risk sharply increases in patients with hemoglobin concentrations less than 6 g/dl. Increased mortality can result from failure of adaptive and compensatory mechanisms to hypoxia to improve oxygen delivery to organs; an exaggerated inflammatory response to severe acute anemia, erythropoietin release, and surgery leading to worsening endothelial dysfunction and organ ischemia; or a poor bone marrow angiogenic and regenerative response (*i.e.*, an impaired endothelial progenitor cell response) resulting from very low hemoglobin concentrations and inflammation.

Image: A. Johnson.

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Other important points to consider in terms of the potential impact of anemia on postoperative outcomes are the patient's age, rapidity of anemia onset, and the hemoglobin-duration deficit product (or duration below a critical hemoglobin value).⁶ Very low hemoglobin concentrations are generally well tolerated in young individuals, but older patients appear to be at a high risk for anemia-related mortality, possibly owing to age-associated limited organ reserve. The duration below a critical hemoglobin value also deserves attention because a delay in administering erythrocytes to improve oxygen delivery is directly related to mortality in patients whose hemoglobin concentrations are below 8 g/dL.⁷

Blood transfusion is the mainstay therapy for moderate-to-severe perioperative anemia; however, administration of blood products is associated with poor outcomes in patients with and without cancer. In those with cancer, blood transfusions can directly (*via* soluble factors) and indirectly (*via* transfusion related immune modulation) induce proliferation and spread cancer cells present at sites of minimal residual disease (tumor margins and dormant tumors).⁸ After transfusions, there is an increase in the concentrations of local (tumor microenvironment) and circulating proinflammatory cytokines and prostaglandin E, which tilt the balance toward immune suppression. At the cellular level, there is a reduction in the function of natural killer cells; a decrease in the proliferation of CD4+, CD8+ T cells, and B lymphocytes; induction of T regulatory cells; and a decrease in maturation and antigen-presenting activity of dendritic cells, which also contributes to a diminished immune function.⁹ Furthermore, administration of blood products may facilitate proliferative and metastatic properties of cancer cells *via* angiogenic and oncogenic factors leaked from stored erythrocytes, a phenomenon associated with the so called storage lesion.¹⁰ Hence, patients with cancer are at a higher risk of tumor recurrence after receiving blood transfusions, which constitutes the "second evil."

Last, the combination of intraoperative or postoperative anemia and blood transfusion, the "third evil," may cause the most harm.³ In the context of an ongoing insult as occurs during surgery, the summation of the response to moderate-to-severe anemia ("first hit") followed by the response to the blood transfusion ("second hit") may cause an exaggerated systemic inflammatory and immune suppressive response, and endothelial dysfunction.¹¹ In the general surgical population, this can translate into a higher risk for early postoperative morbidity and mortality. In patients with cancer, the consequences of inflammation and "immune paralysis" can be seen as an increased risk for recurrence or cancer-specific mortality.

In conclusion, moderate-to-severe anemia and blood transfusions induce marked changes in the homeostasis of several physiological processes, including endothelial function, complement activation, the inflammatory response, and immune function, all of which have been linked to the pathogenesis of end-organ ischemia (particularly in older patients and those with advanced atherosclerotic disease). They have also been

linked to cancer recurrence. Until oxygen delivery can be monitored precisely, perioperative physicians must rely on a hemoglobin value to "safely" transfuse or not patients during and after surgery. The work by de Almeida *et al.*¹ supports previous studies, indicating that perioperative anemia is the predictor of mortality in patients with cancer. Their work indicates that maintaining a hemoglobin concentration above 9 g/dL is prudent in cancer surgery patients. In those patients who are at risk of developing significant anemia during or after surgery (hemoglobin <9 g/dL), preoperative administration of blood transfusions, administration of iron supplements, and minimally invasive surgical techniques may prove helpful, although none has been specifically tested in this context.

Competing Interests

The author is not supported by, nor maintains any financial interest in, any commercial activity that may be associated with the topic of this article.

Correspondence

Address correspondence to Dr. Cata: jcata@mdanderson.org

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