CAGS AND ACS EVIDENCE BASED REVIEWS IN SURGERY. 43

Operative blood loss, blood transfusion and 30-day mortality in older patients after major noncardiac surgery

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The term "evidence-based medicine" was first coined by Sackett and colleagues as "the conscientious, explicit and judicious use of current best evidence in making decisions about the care of individual patients."[1] The key to practising evidence-based medicine is applying the best current knowledge to decisions in individual patients. Medical knowledge is continually and rapidly expanding. For clinicians to practise evidence-based medicine, they must have the skills to read and interpret the medical literature so that they can determine the validity, reliability, credibility and utility of individual articles. These skills are known as critical appraisal skills, and they require some knowledge of biostatistics, clinical epidemiology, decision analysis and economics, and clinical knowledge.

Evidence Based Reviews in Surgery (EBRS) is a program jointly sponsored by the Canadian Association of General Surgeons (CAGS) and the American College of Surgeons (ACS) and is supported by an educational grant from ETHICON and ETHICON ENDO-SURGERY, both units of Johnson & Johnson Medical Products, a division of Johnson & Johnson and ETHICON Inc. and ETHICON ENDO-SURGERY Inc., divisions of Johnson & Johnson Inc. The primary objective of EBRS is to help practising surgeons improve their critical appraisal skills. During the academic year, 8 clinical articles are chosen for review and discussion. They are selected for their clinical relevance to general surgeons and because they cover a spectrum of issues important to surgeons, including causation or risk factors for disease, natural history or prognosis of disease, how to quantify disease, diagnostic tests, early diagnosis and the effectiveness of treatment. A methodological article guides the reader in critical appraisal of the clinical article. Methodological and clinical reviews of the article are performed by experts in the relevant areas and posted on the EBRS website, where they are archived indefinitely. In addition, a listserv allows participants to discuss the monthly article. Surgeons who participate in the monthly packages can obtain Royal College of Physicians and Surgeons of Canada Maintenance of Certification credits and/or continuing medical education credits for the current article only by reading the monthly articles, participating in the listserv discussion, reading the methodological and clinical reviews and completing the monthly online evaluation and multiple choice questions.

We hope readers will find EBRS useful in improving their critical appraisal skills and in keeping abreast of new developments in general surgery. Four reviews are published in condensed versions in the *Canadian Journal of Surgery* and 4 are published in the *Journal of the American College of Surgeons*. For further information about EBRS, please refer to the CAGS or ACS websites. Questions and comments can be directed to the program administrator, Marg McKenzie, at mmckenzie@mtsinai.on.ca.

Reference

1. Evidence-Based Medicine Working Group. Evidence-based medicine. *JAMA* 1992;268:2420-5.

Selected Article

Wu WC, Smith TS, Henderson WG, et al. Operative blood loss, blood transfusion, and 30-day mortality in older patients after major noncardiac surgery. *Ann Surg* 2010;252:11–7.

Abstract

Question: In elderly patients with variable preoperative anemia and volume of blood loss during major noncardiac surgery, does intraoperative blood transfusion reduce the risk of perioperative death? **Design:** Retrospective cohort study. **Data source:** National Surgical Quality Improvement Program database. **Patients:** Veterans aged 65 years or older with a documented preoperative hematocrit (HCT) value who underwent major noncardiac surgery between 1997 and 2004. **Methods:** Propensity score matching was used to adjust for differences between patients who received intraoperative blood transfusions (9.45) and those who did not. **Main outcome:** Association between intraoperative blood transfusion and 30-day postoperative mortality. **Results:** After propensity score matching, intraoperative blood transfusion was associated with mortality risk reduction in patients with preoperative HCT levels lower than 24% (odds ratio [OR] 0.60, 95% confidence interval [CI] 0.41–0.87) and in patients with HCT of 30% or greater who experienced substantial (500–999 mL) blood loss (OR 0.35, 95% CI 0.22–0.56 for HCT levels between 30% and 35.9%, and OR 0.78, 95% CI 0.62–0.97 for HCT levels of 36% or greater). When operative blood loss was less than 500 mL, transfusion was not associated with mortality reductions for patients with HCT levels of 24% or greater and conferred increased mortality risks in patients with preoperative HCT levels between 30% and 35.9% (OR 1.29, 95% CI 1.04–1.60). **Conclusion:** Intraoperative blood transfusion was associated with lower 30-day postoperative mortality among elderly patients undergoing major noncardiac surgery if there was substantial operative blood loss or low preoperative HCT levels (< 24%). Transfusion was associated with increased risk of death for those with preoperative HCT levels between 30% and 35.9% and less than 500 mL of blood loss.

Commentary

Decisions surrounding perioperative blood transfusions are commonplace in surgical practice and have implications for patient outcomes. Studies estimate that 40% of noncardiac surgery patients have preoperative anemia, with which comes an increased risk for postoperative morbidity and death.[1,2] Subsequent blood loss during surgery can exacerbate anemia and may increase the risk of death.[3,4] Blood transfusion is the mainstay of treatment for acute anemia in the operative setting[1] but can be costly and may be overused: in the United States, 13.9 million red blood cell (RBC) units were transfused to 4.9 million patients in 2001, and in 2001/02, the Canadian Blood Services expenditures totaled $638.8 million.[5–7] Determining the candidates who would benefit most from transfusion would have broad clinical implications and change clinical practice.

Wu and colleagues[3] performed a retrospective cohort study using data from a standardized database (National Surgical Quality Improvement Program) to determine whether intraoperative blood transfusions reduce the risk of perioperative death in patients at Veterans' Affairs (VA) centres who underwent major noncardiac surgery and had variable preoperative anemia and volume of blood loss. The study cohort included 239 286 patients from 132 VA centres who underwent surgery between 1997 and 2004 in 8 surgical subspecialties. The investigators compared patients who received blood transfusions with those who did not, using propensity score matching to control for the intrinsic differences between the 2 groups. Propensity score technology aims to reduce the entire collection of background characteristics (confounders or variables that might affect outcomes) to a single composite characteristic that appropriately summarizes the potential collection of confounders. Thus, instead of traditional matching based on a few characteristics, propensity scoring considers multiple characteristics and comes up with a cumulative score for each patient. Patients in different cohorts can be matched based on their individual propensity scores. Propensity scores allow groups to be matched according to variables that can be measured; however, unlike with randomization, groups may not be similar with respect to variables that cannot be measured.

The authors demonstrated a strong association between intraoperative transfusion and lower 30-day mortality in patients with preoperative HCT levels lower than 24% (about 80 g/L). Interestingly, they also demonstrated an increased risk of death when patients with preoperative HCT levels of 30% or greater were transfused, except when the transfusion was because of substantial intraoperative blood loss (500–999 mL). Thus the results of the present study are similar to others, suggesting that RBC transfusion should be restricted to either hemoglobin levels below 70–80 g/L (or HCT levels below 24%), or when there is substantial (500–999 mL) blood loss.

This study represents a critical addition to the literature because it helps to define the population of patients who benefit from blood transfusions owing to its use of a large cohort of perioperative patients and extensive subgroup analyses. There is a growing body of data suggesting that blood transfusions are harmful. In a large randomized controlled trial, Hébert and colleagues[8] showed that there is no benefit and possible harm associated with a liberal transfusion strategy, which they defined as a hemoglobin transfusion trigger of 10.0 g/dL. Patients with active bleeding,

chronic anemia and active angina were excluded from the study by Hébert and colleagues.[8] A systematic review of 17 randomized trials (8 surgical) comparing "restrictive" and "liberal" transfusion triggers found that, although a restrictive strategy was associated with an absolute risk reduction of 33% in patients who received a transfusion, there was no difference in adverse events between the groups. Carless and colleagues[5] concluded that further high-quality clinical trials are needed to delineate the effect of variable transfusion thresholds on adverse outcomes. The prevailing notion from the results of these various studies suggest that blood transfusions do not routinely improve outcomes in anemic patients and have a narrow therapeutic window of benefit.[9] In fact, others have shown that blood transfusions are independently associated with increased risk of death, multiple organ failure and increased infection rates.[10–12]

Wu and colleagues[3] provide a novel perspective by assessing outcomes in relation to both HCT levels and intraoperative blood loss. It attempts to offer more detailed decision-making guidance when patients' hemoglobin levels are between 6 and 10 g/dL, a cohort for whom there is minimal evidence available. In particular, the study suggests that blood transfusions may provide a mortality benefit to patients with a preoperative HCT lower than 24% (about 8 g/dL), irrespective of blood loss, and to those with an HCT greater than 30% in the case of substantial blood loss (> 500 mL). The results of this study, however, can only be generalized to a similar cohort: perioperative patients aged 65 years or older, almost all of whom are men. Although this limits the generalizability to the entire population of perioperative patients, it does focus on a group who are at particularly high risk for adverse events.

Propensity matching is a powerful tool to control for potential biases in retrospective data: the propensity score allows the populations to be "normalized" using variables that the authors deem important. However, this method may not be powerful enough to account for important unknown confounders that can bias the outcome. It does not overcome the fact that the 2 groups were fundamentally different: they differed with respect to the evaluated characteristics. The primary limitation of this study is that it is retrospective and relies on data from a large, nondedicated database. For the most part, transfused patients had many more comorbidities and underwent more complex and longer surgeries than nontransfused patients. Even after propensity-matching, significant differences persisted in important parameters like preoperative HCT, American Society of Anesthesiologists classification, history of myocardial infarction, mean operative time and use of general anesthesia.

Another potential limitation of this study is its reliance on estimated blood loss and the mathematical formula used to calculate it. The formula combines pre- and postoperative HCT, and the amount of packed RBCs transfused. Although these variables are important, the formula neglects the quantity of crystalloid and colloid given intraoperatively, which produces hemodilution and affects the postoperative HCT. However, in the setting of a retrospective review, it does give a reasonable estimate.

Despite the limitations of the study, the point that preoperative HCT and estimated blood loss could potentially be used to identify patients who may benefit from transfusions is important, and further study is needed to broaden the generalizability of these conclusions. In addition, a more accurate method for evaluating preoperative anemia and intraoperative blood loss would make the conclusions more robust. The ideal future study would be a randomized, controlled trial that also considers leukodepletion, blood age, duration of surgery and patient weight among other factors. Transfusions in certain situations are life-saving, while in others they cause harm. Determining optimal transfusion triggers may reduce mortality and morbidity as well as the inappropriate use of blood, an expensive and scarce resource.

Competing interests: None declared.

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