SPECIAL ARTICLE

Canadian Association of General Surgeons, the American College of Surgeons, the Canadian Society of Colorectal Surgeons and the American Society of Colorectal Surgeons Evidence Based Reviews in Surgery – Colorectal Surgery

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for the Members of the Evidence Based Reviews in Surgery Group

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

The Canadian Association of General Surgeons and the American College of Surgeons jointly sponsor a program entitled "Evidence Based Reviews in Surgery". The primary objective of this initiative is to help practicing surgeons improve their critical appraisal skills. Evidence Based Reviews in Surgery has a module covering topics in colorectal surgery. Each academic year, 6 clinical articles are chosen for review and discussion. The articles are selected not only for their clinical relevance to colorectal surgery, but also to cover a spectrum of methodological issues important to surgeons; for example, causation or risk factors for disease, natural history or prognosis of disease, quantifying disease (measurement issues), diagnostic tests and the diagnosis of disease, and the effectiveness of treatment. Both methodological and clinical reviews of the article are performed by experts in the relevant areas and posted on the Evidence Based Reviews in Surgery-Colorectal Surgery EBRS-CRS) website. In addition, a listserv discussion is held where participants can discuss the monthly article. Members of the Canadian Association of General Surgeons (CAGS) and the American College of Surgeons (ACS) can access EBRS-CRS through the Canadian Association of General Surgeons website (www.cags-accg.ca), the American College of Surgeons website (www.facs.org/education/ebrs.html), the Canadian Society of Colon and Rectal Surgeons website (www.cscrs.ca), and the American Society of Colon and Rectal Surgeons website (www.fascrs.org). All journal articles and reviews are available electronically through the website. Surgeons who participate in the monthly packages can receive 6 continuing medical education and/or Maintenance of Certification credits by completing an evaluation and a series of multiple choice questions each month. For further information about EBRS-CRS, readers are directed to the CAGS, ACS, Canadian Society of Colon and Rectal Surgeons, and American Society of Colon and Rectal Surgeons websites or should email the administrative coordinator, Marg McKenzie, at mmckenzie@mtsinai.on.ca

In addition to making the reviews available through the CAGS and the ACS websites, a condensed version of the reviews will be published in the *Diseases of the Colon & Rectum*. Evidence Based Reviews in Surgery is useful in improving your critical appraisal skills, keeping abreast of new developments in colorectal surgery, and, most importantly, you are able to obtain 6 continuing medical education credits each month from anywhere that you have access to a computer. Comments about evidence-based reviews in surgery may be directed to mmckenzie@mtsinai.on.ca

SELECTED ARTICLE

Harlaar JJ, Gosselink MP, Hop WC, et al. Blood transfusions and prognosis in colorectal cancer: long-term results of a randomized controlled trial. *Ann Surg.* 2012;256:681–687.

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QUESTION: Is there a difference in long-term cancer-related and overall survival between patients receiving autologous vs allogeneic blood transfusion during the first colon resection for colon cancer?

DESIGN: This study was a randomized controlled trial.

SETTING: It was a multicenter study that included 15 hospitals in the Netherlands and the United Kingdom.

PATIENTS: Four hundred seventy-five patients accrued between August 1986 and November 1991 were randomly assigned to allogeneic and autologous transfusion groups.

INTERVENTION: Patients were randomly assigned to allogeneic or autologous groups. Patients in the autologous group gave 2 units of blood at least 5 days before surgery so they could receive their own blood, if required. The allogeneic group received third-party blood from a blood bank, if required. Standard rules for transfusion were used for both groups. Packed red blood cells could be given only if the blood loss exceeded 500 mL or hemoglobin concentrations dropped below 10.5g/dL.

MAIN OUTCOME: Overall cancer-specific survival at 20 years was the primary outcome measured.

RESULTS: The overall survival at 20 years after surgery was worse in the autologous group (21%) than in the allogeneic (28%; $p = 0.041$; log-rank test). Cox regression, allowing for tumor stage, age, and sex, resulted in a HR (autologous vs allogeneic group) for overall mortality of 1.24 (95% CI 1.00–1.54; $p = 0.051$). Colorectal cancer-specific survival at 10 years for the whole study group was 48% and 60% for the autologous and allogeneic group ($p = 0.020$; log-rank test). The adjusted HR was 1.39 (95% CI 1.05–1.83; $p = 0.045$).

CONCLUSION: At long-term follow-up, patients with colorectal cancer did not benefit from autologous transfusion compared with standard allogeneic transfusion. On the contrary, the overall and colorectal cancer-specific survival rates were significantly worse in patients in the autologous transfusion group.

COMMENTARY: Many patients with colorectal cancer present with anemia. A wealth of data, collected over decades, demonstrate that perioperative blood transfusion in these patients is associated with short-term infectious complications and poorer cancer-related outcomes. These findings have been recently updated in a systematic review[2] of 55 studies that included more than 20,000 patients who underwent colorectal surgery over 3 decades. Explanations for these poor outcomes related to transfusions include the limited ability of an anemic patient to respond to curative cancer treatment, the immunosuppressive effect of transfused blood that predisposes to infectious complications and cancer recurrence, and selection bias because patients with more aggressive tumors or more limited reserve to recover from cancer surgery are more likely to be judged to need a blood transfusion. Thankfully, time and research has increased the safety of allogeneic blood, and leukocyte reduction protocols have reduced, but not eliminated, transfusion-related immunomodulation associated with allogeneic blood transfusions. It is not clear what the effect such protocols have had on cancer recurrence and mortality, especially in patients with colon cancer, which makes this study interesting to those practicing in the field.

Harlaar et al[3] used follow-up data from a historic randomized controlled trial to determine the long-term all-cause survival and cancer-specific survival in patients randomly assigned to either autologous or allogeneic blood transfusion at the time of their primary operation. In the original report, published in 1993, the authors reported no difference between the 2 treatment groups, but blood transfusion, whether it was autologous or allogeneic, was associated with decreased survival. After 20 years of follow-up, patients randomly assigned to the autologous blood donation group were found to have a worse outcome with respect to both long-term all-cause and cancer-specific mortality. The authors theorize that anemia from the predonation of blood may have had an effect on tumor growth. Unfortunately, there are few data or little further analysis of this group of patients. It is noteworthy, however, that significantly more patients in the autologous transfusion group underwent 1 or more transfusions (74% versus 56%). The methodological design of the original study was robust enough so that the results of the study are relevant to current day practice. Blinding of surgeons or patients to blood transfusion, and specifically autologous blood donation, was not possible. However, because the primary and secondary outcomes were objective (ie, overall and cancer-specific mortality), this is not a major concern. Furthermore, to help minimize variation in transfusion rates within patients and groups, standard blood transfusion rules were used to guide transfusion. These rules proved to be close to current day ASA recommendations that a red blood cell transfusion is indicated for a hemoglobin of less than 6 g/dL and usually unnecessary for a hemoglobin of >10 g/dL.[4]

In the 20 years since the trial was performed, there have been many changes in the surgical and medical management of patients who have colorectal cancer. In particular, laparoscopic surgery is more common as acknowledged by the authors in the conclusion. Most patients with rectal or rectosigmoid cancer now receive neoadjuvant and adjuvant therapy. These may decrease the need for transfusion. In a series reported by the Cleveland Clinic[5] in 2004, only 5% of patients undergoing a laparoscopic colorectal cancer procedure and 10% of patients undergoing an open operation received a transfusion. In the present study, 56% of the patients in the allogeneic blood group received transfusions and 65% of patients in the autologous donation group received transfusions.

This study presents a compelling reason to discourage preoperative autologous blood transfusion in patients

undergoing surgery for colorectal cancer. Although some patients may inquire about autologous donation of blood before cancer surgery, this is an unusual event. The rate of viral infectious transmission through blood transfusion is extremely low and unlikely to make a large impact on the patient in their decision making before surgery. However, the data from this study are important because periodic concerns about blood products (ie, prior disease or other potential emerging infections) may revive patient interest in the autologous transfusions in the future, and the data from this high-quality study can be helpful in informing this discussion in the future.

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