Bleeding Is Rarely Good for You

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In a careful statistical analysis of 651,775 patients undergoing elective noncardiac, non-neurological, noncarotid surgery in the American College of Surgeons National Surgical Quality Improvement Program (NSQIP) database between 2005 and 2009, Kamel and colleagues have reaffirmed that bleeding is bad, and that more bleeding is worse, at least in the intraoperative period. Patients who received >4 units of packed red blood cells or whole blood had an ∼2.5-fold increased risk of a subsequent stroke or Q-wave myocardial infarction (MI), independent of a multitude of other risk factors. The relationship between blood loss and postoperative MI or stroke was related to the severity of bleeding: For each unit of intraoperative transfusion with packed red blood cells or whole blood, the risk was reported to increase by ∼1.1-fold (95% confidence interval, 1.10–1.13). In a sensitivity analysis reported in their Discussion section, these results were unchanged when “limited to large intraoperative bleeding: For each unit of intraoperative transfusion with packed red blood cells or whole blood had an ∼2.5-fold increased risk of a subsequent stroke or Q-wave myocardial infarction (MI), independent of a multitude of other risk factors. The relationship between blood loss and postoperative MI or stroke was related to the severity of bleeding: For each unit of intraoperative transfusion with packed red blood cells or whole blood, the risk was reported to increase by ∼1.1-fold (95% confidence interval, 1.10–1.13). In a sensitivity analysis reported in their Discussion section, these results were unchanged when “limited to large intraoperative transfusions in patients without baseline anemia.”

This study must be interpreted in the context of another study from the NSQIP dataset. Glance and colleagues reported that a 1- to 2-unit intraoperative blood transfusion was not significantly associated with cardiac or neurological complications in an analysis limited to 10,100 patients who underwent general, vascular, or orthopedic surgery. The adjusted risk of cardiac complications (odds ratio, 1.31; 95% confidence interval, 0.88–1.95) was not inconsistent with the findings of Kamel and colleagues. But, in this report, the risk of central nervous system complications was actually significantly lower (odds ratio, 0.68; 95% confidence interval, 0.34–1.38) in patients who received 1 to 2 units of intraoperative blood. These 2 studies, put together, indicate that a lot of bleeding is bad and a little bit is probably not good.

The authors acknowledge some of the limitations of their study design. The database that they searched had no information regarding the perioperative use of antiplatelet medications. The database could not distinguish hemorrhagic as compared with ischemic strokes, although most perioperative strokes are thought to be ischemic.

More importantly, the NSQIP database also lacks information about the intraoperative courses of the patients in it. Even if bleeding is not good, it is unclear whether the 2.5-fold increase risk of complications related to major intraoperative bleeding is more a function of the associated hypotension than of a specific reduction in oxygen-carrying capacity. For example, data from decades ago clearly showed that marked intraoperative hypotension is associated a higher risk of postoperative cardiac events. We know from a prior analysis of NSQIP that preoperative anemia, even if mild, is associated with an ∼1.4-fold increased risk of postoperative morbidity or mortality. In that study, from the same database, the risk of cardiac morbidity was increased 1.44-fold in patients with minor preoperative anemia (hematocrit reduced but above 29%) and 1.52-fold in patients with moderate to severe preoperative anemia (hematocrit 29% or less), suggesting that one third of the increase in cardiac risk noted by Kamel and colleagues might somehow be linked to diminished oxygen-carrying capacity rather than to hypotension. By comparison, central nervous system complications were not increased even by moderate to severe preoperative anemia. This finding, combined with the data of Glance et al, suggests that perhaps all of the increased stroke risk associated with intraoperative bleeding may be related to hypotension rather than to a diminution of oxygen-carrying capacity.

But the major shortcoming of the Kamel study is its reliance on NSQIP’s definition of stroke or Q-wave MI based on data recorded during routine, nonprotocol driven, clinical care. Although the number of undiagnosed strokes may be small, because stroke is generally defined clinically and not based on routine postoperative screening tests, the diagnosis of postoperative MI depends greatly on the diagnostic methods used. In the study of Kamel et al, postoperative Q-wave MI and postoperative stroke were about equally common. So, what do we get if we compare the ∼1:1 ratio of MI to stroke in the Kamel study with other recent large studies that used different diagnostic criteria or methods? First, it is important to look at the way patients were followed postoperatively in prospective studies, such as in our study of cardiac risk in noncardiac surgery, the large PeriOperative ISchemic Evaluation (POISE) trial, and a trial of different perioperative transfusion strategies. In all 3 prospective studies, patients were followed daily by study personnel and had 2 or more postoperative electrocardiograms and blood tests—creatine kinase-MB in our earlier study and troponin levels in the 2 later studies—done routinely and at the time of any suspicious event. Because all 3 studies included daily postoperative evaluations by study personnel, all likely diagnosed some small strokes that may have been missed in NSQIP.
What did these 3 studies find? Our ratio of all MI to stroke was \( \approx 3:1 \) if patients undergoing carotid endarterectomy were excluded, as were by Kamel and colleagues,\(^1\) and the ratio of non–ST-elevation MI to ST-elevation MI was \( \approx 5:1 \). In POISE, the ratio of postoperative MI to postoperative stroke was 7:1. In the Carson study, the ratio was 5.5 postoperative MIs for each postoperative stroke. So, NSQIP, which may well have missed some small postoperative strokes, undoubtedly missed \( \approx 80\% \) of postoperative MIs by modern diagnostic criteria. As a result, Kamel and colleagues clearly have substantially underestimated the absolute risk of postoperative MI attributable to perioperative hemorrhage and may also have substantially underestimated the relative risk resulting from postoperative hemorrhage.

In their elegant randomized trial, Carson and colleagues\(^9\) showed no overall benefit from a liberal compared with a conservative strategy for perioperative blood transfusion in patients whose hemoglobin level was \(<10 \text{ gm/dL} \) after hip fracture surgery. Patients treated with the restrictive strategy were twice as likely to get transfusions because of chest pain (0.9% versus 0.4%), \( \approx 3 \) times as likely to receive transfusions because of tachycardia or hypotension (12.2% versus 4.3%), and 10 times as likely to get transfusions because of heart failure (1% versus 0.1%). Only the latter 2 differences were statistically significant. Interestingly, the risk of postoperative MI was increased by \( \approx 65\% \) (nonsignificant) with the restrictive transfusion strategy, but the risk of stroke was actually lower (again, not significantly) with the restrictive strategy, but the risk of stroke was \( \approx 300 \) times larger. But, once again, the data suggest no increase in stroke based on diminished oxygen-carrying capacity.

As noted by Kamel and colleagues, 2 small randomized trials\(^{10,11}\) totaling 511 patients found no differences in the risk of bleeding regardless of whether patients received placebo or aspirin at 75 mg/d.\(^{10,11}\) In the Mantz study,\(^10\) the number of postoperative events was too small for meaningful analysis. In the Oscarsson study of higher-risk patients,\(^11\) adverse cardiac events were less likely in patients receiving aspirin (2 major events compared with 10 major events in the placebo group), but the risk of stroke or transient ischemic attack was identical in the 2 groups.

The American College of Chest Physicians publishes evidenced-based clinical practice guidelines for the perioperative management of antithrombotic therapy, the last of which was published in 2012.\(^12\) Although each iteration of these guidelines is logical and consensus-driven, each is based on weak data, essentially none from randomized trials. As noted by Kamel and colleagues, this problem cries out for better data, which can be obtained only from placebo-controlled randomized trials. And the problem is getting even more important. We know that noncardiac surgery in the first 4 to 6 weeks after coronary stenting is associated with a markedly increased risk of in-stent thrombosis.\(^13\) We also know that longer dual-agent antplatelet therapy is needed with drug eluting stents, which then are probably somewhat better than bare metal stents.\(^14\) But, despite sensible interim recommendations based on nonrandomized data,\(^{12,13}\) we really do not know at all how best to manage these patients through noncardiac surgery, be they soon or long after a bare metal or drug-eluting stent. It simply is not appropriate for us to keep tap dancing with recommendations whose scientific basis is no more sound than a variety of treatment guidelines that have long since been abandoned based on careful randomized trials. So, I join with Kamel and colleagues in calling for 3 different perioperative trials: how best to manage patients who are on aggressive antplatelet therapy after coronary stenting; how best to manage patients who are treated long-term with aspirin or other antiplatelet agents for the secondary prevention of myocardial infarction or ischemic cerebrovascular events; and how best to manage patients who have atrial fibrillation and are receiving prophylactic anticoagulation to prevent embolic stroke. The number of at-risk patients undergoing noncardiac surgery each year is simply too high for us to continue to let these questions remain unanswered.

Until that time, what conclusions can we draw? First, we have reasonable guidelines to follow for now, even though they are supported by weak data.\(^{12,13}\) Second, I see no evidence that diminished oxygen-carrying capacity itself causes postoperative stroke. Rather, it seems much more likely that the risk of perioperative stroke is related to hypotension, which often can be caused by bleeding. Third, both anemia and bleeding appear to raise the risk of postoperative MI. The absolute increase in risk is undoubtedly much larger than what was estimated by Kamel and colleagues, and the relative increase may be larger as well.

**Disclosures**

None.

**References**


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