A recent multidisciplinary investigator’s forum on blood management, called “Inflammation, Hemostasis and Blood Conservation Strategies,” Bruce Spiess, MD, director of Virginia Commonwealth University’s Reanimation Engineering Shock Center in Richmond (VCURES), made what might, at first blush, appear to be an audacious request: “We need somewhere between 50 to 100 large-scale clinical trials.” He was requesting new research to help define at what point transfusion should take place for patients undergoing cardiac and other surgical procedures. The event, held at Emory University School of Medicine in Atlanta from September 30 to October 1, was sponsored by Bayer Pharmaceuticals.

Bayer makes aprotinin (Trasylol®), a protease inhibitor that helps to maintain hemostasis by shutting down inflammation associated with transfusion. Aprotinin is often used in cardiac surgery and, increasingly, in orthopedic surgery to reduce blood loss. In clinical trials, aprotinin has reduced the need for transfusion by 35% to 48%, and the reduction in blood loss, Dr. Spiess said, has been as high as 80%. The largest meta-analysis, by Sedrakyan et al., indicated an overall reduction of 39%.

Why the urgency? After all, according to one forum attendee, Steven Steinhubl, MD, Associate Professor of Medicine at the University of Kentucky College of Medicine, the adage for interventional cardiologists putting stents into coronary arteries, has been this: It’s easier to replace blood than to replace myocardium.

Until recently, it has been common practice to combine femoral artery access for balloon catheters and stents with drugs that are designed to calm inflamed acute coronary syndrome (ACS) blood components, often leading to the loss of a few liters of blood into the draping or, worse yet, into the leg. This bleeding has been considered a relative non-issue; the stock solution has been to infuse just a few units.

Newer compelling data, however, are turning blood loss into a frontline concern. At the European Society of Cardiology, 2005 Congress, held in Stockholm, Sweden (September 3–7), professor Salim Yusuf, MD, from McMaster University in Hamilton, Ontario, Canada, presented data on the OASIS 5 study in a Hot Line session. OASIS 5, the largest ACS trial on record with more than 20,000 patients, compared an older and a newer low-molecular-weight heparin, fondaparinux (Arixtra®), GlaxoSmithKline) and enoxaparin (Lovenox®, Sanofi-Aventis). Major bleeding was a primary endpoint.

Dr. Yusuf’s analysis of the risks incurred by ACS patients with non-ST-segment elevation who experienced serious bleeding showed that the consequences persist far beyond the duration of bleeding itself. Looking at the impact of nonfatal myocardial infarction (MI), refractory ischemia, and major or minor bleeding on the crude odds ratios of mortality risk at 180 days, he found that the risk of dying was increased by 410% in patients who had experienced major bleeding. Only nonfatal MI had a greater impact (560%). Even minor bleeding more than doubled the mortality risk.

How strong is the evidence pointing to transfusions as a source of risk? Dr. Spiess noted that there is only one randomized trial of transfusion outcomes. This trial compared 10 g/dl with 7 g/dl as transfusion triggers in 838 critically ill ICU patients. The hospital mortality was significantly higher with 10 g/dl. Other research has shown that red blood cell (RBC) transfusions increase the risk of serious bacterial infection and metastases in colon cancer resections; moreover, the number of units transfused is the leading predictor of length of hospital stay and complications in coronary artery bypass graft (CABG) surgery.

In 2004, Dr. Spiess published findings on 1,720 patients from an evaluation of data from 1990 to 1995 from six clinical trials at 37 medical centers in the U.S., Denmark, and Israel. His analysis of the trials, which were designed to assess the ability of aprotinin to reduce the need for transfusion, showed a five-fold increase in mortality in patients (n = 284) who received platelet transfusions during CABG surgery. The transfusions extended the surgical time by 1.2 hours, and nearly 20% of the patients who had undergone transfusion needed more surgery, compared with 2% of those not receiving transfusions.

The following question arises, however: Do these data establish a causal relationship? Is it possible that patients who received transfusions were merely sicker and therefore had worse outcomes? After adjusting for confounders with sophisticated statistical methods, Dr. Spiess still found that bleeding remained an independent predictor of worse outcomes.

He listed several potential mechanisms of harm from transfusions. For instance, allogenic RBC transfusions, which contain high levels of numerous different cytokines, bradykinin, serotonin, and live white blood cells (WBCs)—if not white cell-reduced—are profoundly inflammatory. Adverse consequences include an increased incidence of postoperative infection, pneumonia, dehiscence, and osteomyelitis in joint replacements. Other sources of harm include transfusion-related acute lung injury and reperfusion injury.

Don’t the benefits of allogenic transfusions far outweigh the risks? The rationale for the transfusion of banked RBCs has always been to improve tissue oxygen delivery. Under normal conditions, erythrocytes can unload up to a maximum of 26% of their total oxygen, but the maximum oxygen release for banked blood is probably only about 6% or less, Dr. Spiess explained. Worse yet, the oxygen affinity of stored cells is so high that they sometimes even pull oxygen away from plasma or other RBCs before they pass through the lungs. For this reason and others, even though banked blood can lead to restored mixed venous saturation, it perfuses the capillary microcirculation very poorly.

In the interim, we can conclude that recommended hemoglobin level triggers are actually too high, but the huge data gap behind Dr. Spiess’s call for additional trials prevents an

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answer to the all-important question, “Which patients should get transfusions when?”

His solution in his own hospital, over a three-year period, has been to reduce the number of transfusions during the entire length of stay for all cardiac surgical patients from a high of 74% down to 14%–18%. For cardiac surgery, he has relied on physiological triggers based on actual individual oxygen deficits (less than 60% venous oxygen saturation, pH below 7.2, and lactate levels above 2 or 2.5 mg/dl) while also taking into account signs of myocardial ischemia or neurological dysfunction. All of this weakens the existing rationale for transfusions. He adds:

We are saying that from our data, they don’t generally help—but we have nothing else. If it helps, it helps marginally and in very small amounts. We may be fooling ourselves, but maybe in critical instances a small amount is enough to get the patient out of trouble. We don’t know what small amount of increased oxygen delivery is necessary or critical for tissues in need. We need big studies to find out.

New support for the use of aprotinin in CABG surgery emerged in October at the annual meeting of the American Society of Anesthesiologists in Atlanta, Georgia. In a study funded by the Department of Anesthesiology at Columbia University College of Physicians and Surgeons, a research team at the university’s medical center in New York City assigned 96 non-diabetic CABG patients to three groups: 28 patients received a full dose of aprotinin, 33 received a half dose, and 35 received no aprotinin. The team, under Robert J. Frumento, PhD, was trying to verify positive effects of aprotinin on glucose levels in humans that had been observed in laboratory studies.

For diabetic patients undergoing CABG surgery, abnormally high levels of blood glucose can lead to serious complications, including cardiac disease, renal dysfunction, retinal damage, and an infection risk that is raised by as much as 86%. Hospital stays and costs go up as well. Among the half million patients who undergo cardiac surgery in the U.S. every year, about a third have diabetes and many others are likely to have impaired glucose tolerance.

In this study, blood was taken at three intervals: after anesthesia, 30 minutes into CABG surgery, and after the surgery. The patients receiving aprotinin had 24% lower blood glucose levels and decreased perioperative insulin resistance than patients not receiving aprotinin.

REFERENCES