Valid Comparisons of Antifibrinolytic Agents Used in Cardiac Surgery

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Bleeding is a major source of morbidity and mortality after cardiac surgical procedures. Patients who return to the operating room for bleeding have a 4-fold increase in mortality and a similar increase in the rate of sternal infection. The significance of this issue is underscored by the fact that patients undergoing cardiac surgery consume up to 30% of the nation’s blood supply. During massive hemorrhage resulting from trauma, the life-saving benefits of blood transfusion are well documented. However, in the more common setting of elective blood and blood component transfusions in intensive care units using arbitrary transfusion triggers, the benefits of transfusion are not well established and may have a net negative influence on outcomes. Indeed, the overt dangers of transfusion are unequivocal (hepatitis C, HIV, fever, infection, increased costs, transfusion reaction), and evidence of the covert dangers of blood transfusion (prolonged intensive care unit stay, increased mortality, increased morbidity) after cardiac surgery is persuasive. Because both bleeding itself and the transfusions administered to compensate for blood loss have an untoward impact on outcomes, there is strong motivation to decrease the occurrence of bleeding associated with cardiac surgical procedures in the first place. In this regard, the Society of Thoracic Surgeons Workforce on Evidence Based Surgery, in conjunction with the Society of Cardiovascular Anesthesiologists, recently published a comprehensive guideline outlining appropriate methods for blood conservation in cardiac surgery.

Recently, Mangano et al published the short-term and longer-term results of the same observational study comparing the 3 antifibrinolytic agents available for use in cardiac surgical patients (aprotinin, e-aminocaproic acid [EACA], and tranexamic acid [TXA]) with control patients who received neither of these agents. These studies caused considerable concern among cardiac surgeons and regulatory agencies because the authors concluded that aprotinin was associated with a higher risk-adjusted incidence of renal failure, perioperative stroke, myocardial infarction, and long-term mortality compared with control patients. However, the underlying methods of analysis used in both of these reports have been criticized. In particular, the “propensity matching” did not adjust for the most important bias in the selection of one agent rather than another (aprotinin versus EACA or TXA) but rather considered the less relevant propensity for using any of the 3 agents versus no agent. Apart from this apparent flaw in the analytical methods, unfortunately, details of the propensity analysis or the multivariate analysis are not provided in the methods section of the original article. There was no indication that important factors such as cardiopulmonary bypass time and the use of inotropic drugs preoperatively were considered in the analysis. Thus, the data presented in the studies by Mangano et al cannot refute the hypothesis that surgeons selected aprotinin (rather than EACA or TXA) preferentially (as is common practice) in higher-risk, more complex, more difficult cases in which bleeding was more likely. In fact, the patients who received aprotinin were 5 times as likely to have previously had a coronary artery bypass graft surgery than control subjects and >2 times as likely to have had a previous coronary artery bypass graft surgery than the patients who received TXA or EACA. These patients would be expected to have higher morbidity and higher short-term and long-term mortality quite unrelated to the antifibrinolytic agent used. Mangano et al may not have adequately controlled for this important source of bias and appeared to inadequately consider the results of randomized controlled trials with findings disparate from their own.

The report by Brown et al in this issue of Circulation presents the results of a meta-analysis of randomized trials comparing the effectiveness and adverse outcomes of the 3 antifibrinolytic agents most commonly used to decrease bleeding after cardiac surgery. The key findings of this timely study were that all 3 antifibrinolytic agents significantly reduce blood loss after cardiac surgery. However, aprotinin was significantly more effective in reducing bleeding than EACA or TXA. Furthermore, aprotinin was the only one that significantly decreased the likelihood of returning to the operating room after cardiac surgery to control bleeding. None of the agents was associated with an increased risk of dialysis dependent renal failure, mortality, or stroke. Aprotinin, but neither of the other 2 agents, was associated with an increased risk of presumably transient renal dysfunction because it did not include an increased risk of progression to dialysis or death. The results of this study are in general agreement with the large body of published literature evaluating the effectiveness and adverse outcomes associated with the use of these agents in cardiac surgery. For example, at
least 28 studies were recently reviewed in a comparison of high-dose aprotinin with control in patients having isolated coronary artery bypass graft surgery using the number of patients transfused as the primary outcome variable. Both the meta-analysis and most of these studies demonstrated a highly significant reduction in blood transfusion in aprotinin-treated patients. In patients who underwent reoperative coronary artery bypass surgery, valve surgery, or combined coronary artery bypass graft surgery/valve operations, the results were similar. In general, the evidence supporting the use of the lysine analogues EACA and TXA as a method to limit the need for blood transfusion after cardiac procedures is less robust than the evidence for aprotinin. However, significant reductions in the number of patients transfused have been noted in patients who underwent various cardiac surgical procedures requiring cardiopulmonary bypass when lysine analogues were compared with placebo. Reexploration for bleeding occurs in <5% of patients after cardiac surgery, but it usually is indicative of clinically significant surgical bleeding and is associated with an increase in operative mortality and morbidity. In 17 studies comparing high-dose aprotinin with control and 11 studies comparing TXA with control, aprotinin but not TXA was consistently associated with a significant reduction in the need for reexploration.

The efficacy of aprotinin and, to a lesser but still significant degree, the efficacy of the lysine analogues TXA and EACA in reducing bleeding after cardiac surgery are well established. The important question is whether the risk of using these agents outweighs the benefit and, in particular, whether the apparent superior efficacy of aprotinin outweighs any risks associated with its use. A thorough review of the literature documents that the safety profiles of aprotinin and the lysine analogues are both excellent. In a meta-analysis of 35 published, randomized controlled trials of aprotinin compared with placebo (3879 coronary artery bypass graft surgery patients), there was no significant increased or decreased mortality, myocardial infarction, or renal failure. Aprotinin actually was associated with a reduced risk of stroke (relative risk, 0.53; 95% CI, 0.31 to 0.90). The evidence-based review published by the Cochrane Collaboration of adult cardiac surgery patients included 2828 patients randomized to aprotinin, and there was no significant increase in operative mortality compared with placebo. In 20 trials that reported relevant data, there was no significant increase in myocardial infarction in 1871 patients randomized to aprotinin compared with 1117 patients given placebo. Aprotinin was not associated with an excess risk of adverse effects, including thromboembolic events and renal failure.

The study by Brown et al illustrates an important distinction in the potential effects of aprotinin on renal function. Aprotinin was associated with a (presumably transient) increase in creatinine but not a significant increase in the need for dialysis (permanent renal failure). Two recent observational studies and one meta-analysis also suggest that aprotinin may be associated with renal dysfunction after cardiac procedures. However, as discussed above, one of these studies appears to suffer from serious methodological flaws, and the study by Karkouti et al lumped renal dysfunction (transient elevation in creatinine) with dialysis-dependent renal failure in the definition of renal “dysfunction.” Another limitation of this study was that 24% of the patients who received aprotinin could not be matched to those who received TXA, and there was a markedly higher risk of perioperative hemorrhage in the unmatched patients who received aprotinin. The authors of this propensity score case-control comparison of aprotinin and TXA acknowledged that this finding illustrated the current surgeon bias for using aprotinin in the highest-risk patients. This source of bias is difficult to exclude from nonrandomized studies, regardless of the statistical methods used, because important confounder covariates are often neither measured nor measurable. The Letter to the Editor by Brown et al recently published in the New England Journal of Medicine appears to present the same data concerning the effect of aprotinin on renal function as the data presented in the study by the same authors in this issue of Circulation. In their previous meta-analysis published in 1999, the trend toward increased renal dysfunction associated with high-dose aprotinin was not significant. The present meta-analysis has been extended to include studies of both EACA and TXA. Prospective randomized trials of aprotinin after periods of circulatory arrest indicate that although aprotinin may lead to a transient increase in creatinine, its use was not associated with an increased risk of dialysis or severe renal dysfunction. In a study of 853 patients after complex aortic surgery including periods of hypothermic circulatory arrest, aprotinin use was not associated with renal dysfunction or failure. In another large meta-analysis of prospective randomized trials of aprotinin recently published by Sedrakyan et al, there was no increase in renal dysfunction/failure in aprotinin-treated patients.

In addition to the issue of any potential for renal toxicity, one must consider other safety issues with the use of antifibrinolytic agents in cardiac surgery. Because aprotinin is a bovine protein, hypersensitivity reactions may occur when this drug is administered to human patients. During an initial exposure to high-dose aprotinin, <0.1% of patients will experience a hypersensitivity reaction, and 50% of these will be anaphylaxis. The rate of hypersensitivity reactions increases to 5% if patients are reexposed to aprotinin within 6 months of initial dosing. Patients themselves or their healthcare providers may not be aware of previous exposures to aprotinin, so an appropriately high index of suspicion, as well as some research, may be necessary to identify patients who may have been exposed to the drug previously. This point deserves emphasis because aprotinin may be used for a variety of surgical procedures other than cardiac surgery and is used in some formulations of fibrin glue. In either of these cases, the history of previous exposure to aprotinin may go unrecognized.

Some of the concerns regarding the safety of antifibrinolytic agents in cardiac surgery are not unique to this class of drugs. Most trials of efficacy are not powered to discover significant but infrequent causes of morbidity associated with pharmaceutical drug use. Although the International Multi-center Aprotinin Graft Patency Experience (IMAGE) trial found no difference in internal mammary artery graft patency in patients treated with aprotinin compared with placebo,
there was a decrease in saphenous vein graft patency associated with aprotinin, but only in non-US sites. Multiple other trials did not document a significant difference in graft patency associated with aprotinin use, but these studies were not powered to find evidence of these uncommon potential sources of morbidity. These findings underscore the need for phase IV studies to evaluate drug safety in addition to phase III studies to document drug efficacy.

In summary, the weight of the evidence indicates that aprotinin appears to be at least as effective as TXA and EACA in preventing bleeding and decreasing the need for blood transfusion after cardiac surgical procedures. Considering all of the available evidence, aprotinin may be associated with a higher risk of renal dysfunction, particularly in patients with preexisting renal disease. It has not been well established that aprotinin is associated with a higher risk of permanent renal failure requiring dialysis in patients with normal preoperative renal function. Aprotinin does appear to be more effective at decreasing the need for surgical reexploration in patients who undergo complex surgical procedures. Therefore, the use of aprotinin must be governed by an appreciation of its inherent risks and benefits. In patients at high risk of bleeding after cardiac surgery, it may be prudent to use all reasonable measures, including aprotinin, in an attempt to decrease the amount of postoperative bleeding and to decrease the need for allogeneic blood and blood product transfusion. More important, a comprehensive approach to blood management in cardiac surgery has clearly been shown to decrease the need for blood transfusion, and antifibrinolytic agents are important components, but only a subset, of the recommended multimodality interventions to conserve blood in cardiac surgery.

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References


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