Controversy of Antifibrinolytic Agents in Cardiac Surgery

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LEARNING OBJECTIVES:

1. To review the evidence-based efficacy and safety of antifibrinolytic agents.
2. To discuss the meta-analysis of head-to-head comparison of antifibrinolytic agents.
3. To appraise the current options of antifibrinolytic use in cardiac surgery

BACKGROUND:

(Anesth Analg 2008;106:●●●-●●●)

Three antifibrinolytics have been routinely used during cardiac surgery, including aprotinin (AP), tranexamic acid (TA), and aminocaproic acid (EACA). When compared to placebo or inactive control, each of these antifibrinolytics has individually been shown to reduce blood loss in patients undergoing cardiac surgery. The number of published randomized placebo-controlled trials is greatest for aprotinin and least for aminocaproic acid, and it has been suggested that aprotinin should be the agent of choice since its evidence base is largest. In addition, aprotinin has been shown in some, but not all, meta-analyses, to reduce the risk of stroke when compared to placebo. However, the more important contemporary question is not whether aprotinin performs better than placebo, but whether it provides better outcomes relative to a comparable alternative–either tranexamic acid or aminocaproic acid. Given that over 1 million cardiac surgeries are performed worldwide and antifibrinolytics are used routinely during cardiac surgery in most centers, the need for clarity on this issue is urgent.

This debate has become particularly salient since the release of three publications related to two observational studies and one unpublished observational study comparing the risks of aprotinin with tranexamic acid or aminocaproic acid. The studies by Mangano et al. were based on a large surgical database derived from 69 institutions around the world, including 4374 patients. The studies raised safety concerns about aprotinin, in particular with respect to increased postoperative risk of renal dysfunction, myocardial infarction, heart failure, cerebrovascular events and increased 5-year mortality. A smaller, case-matched database study by Karkouti et al. in 898 high risk patients from a single institution also raised concerns of renal safety. After these studies triggered renewed FDA deliberations about the safety of aprotinin on September 2006, the FDA was informed by the Bayer Pharmaceutical of an additional unpublished observational safety study (i3 study, Schneeweiss et al.) involving close to 67,000 patients with preliminary results suggesting that, in addition to renal dysfunction, aprotinin may increase risk of death, congestive heart failure, and strokes. Other trials have not confirmed the increased risk of death, stroke, or myocardial infarction. These discrepancies may be due to power issues, differences in adjusting for confounders, and differences in comparators (active vs inactive control group). Warnings were issued from regulatory bodies in various countries emphasizing the need for judicious use of aprotinin with appropriate surveillance. Some experts suggested there was little need for change in practice, while others suggested that routine aprotinin use should be abandoned in favor of safer alternatives. Overall, the mixed messages have caused confusion, and objective clarification of the evidence is required before reasoned discussion can converge on evidence-based recommendations for practice.

A follow-up FDA public joint meeting of the Cardiovascular and Renal Drugs Advisory Committee and the Drug Safety and Risk Management Advisory Committee was held in September 12, 2007 to review the totality of evidence on the safety of aprotinin. FDA independently reanalyzed the data from the above studies by its Quantitative Safety and Pharmacoepidemiology group. The FDA concluded that the evidence for renal effect, including renal failure consistent; there is evidence for long-term mortality effect; but the effects for cardiovascular, cerebrovascular, and in-hospital death outcomes are not statistically demonstrated. The recommendations at that time were to keep the same safety warning as in September 12, 2006 of increasing risk of renal dysfunction and may increase the need for dialysis in the perioperative period after aprotinin use; indicated in cardiac surgical patients with increased risk of blood loss and blood transfusion; and the anaphylactic reaction with prior exposure; and of Bayer Pharmaceutical to perform randomized controlled trial on aprotinin to alteratives. However on October 19, 2007, FDA was informed of the Data Safety Monitoring Board's recommendation to stop patient enrollment in the Canadian BART study (a randomized controlled trial of the use of antifibrinolytics in high-risk cardiac surgical patients),

because of the consistent increased 30-day mortality in the aprotinin group in comparison to TA or EACA at the interim analysis near the completion of this study. On November 5, 2007, FDA requested market suspension of aprotinin, as one FDA officials was quoted, "F.D.A. could not identify a specific patient population where the benefits of using Trasylol could outweigh the risks." At the present time, the data of the BART study is being analyzed and pending submission for publication.

WHAT ARE THE BENEFITS AND RISKS OF AP VERSUS TA/EACA?

We recently performed a comprehensive meta-analysis of all available direct comparative trials. Bainbridge et al. (27 randomized and 2 observational comparative trials; 8590 patients) suggests that AP provides no proven clinical advantage over TA/EACA. The number of patients exposed to allogeneic RBC transfusion or any blood product transfusion is similar with AP or with TA/EACA when either randomized or nonrandomized trails are considered. When units of blood transfused is considered, at best, only modest reductions in total red blood cells administered were observed in the AP group versus TA/EACA (0.16 U/patient, ranging from a minimum of 0.07 U to maximum of 0.2 U per patient), which most clinicians would consider to be clinically insignificant. The results were also consistent across low-risk versus high-risk patient studies. On the other hand, the balance of the evidence suggests that, compared with TA/EACA, AP might cause harm including death, stroke, myocardial infarction, or renal dysfunction.

ARE THESE RESULTS BIASED?

While significant controversy remains regarding the validity of the current evidence base for quantifying the magnitude of risk of AP versus TA/EACA, it is important to put these risks into context. It is widely accepted that randomized trials represent the highest standard for determining treatment effects. However, the limitations of randomized trials in providing sufficient power to detect infrequent adverse events is also widely recognized and high quality observational trials have been embraced to fill gaps in the evidence where randomized trials fail to inform. Many randomized trials reported only bleeding and transfusion outcomes. The lack of statistical significance for estimates of harm does not prove lack of harm, but rather the wide confidence intervals show that the possibility of harm cannot be ruled out (insufficient data). Overall, even conservative interpretation of the totality of the evidence base directly comparing AP versus TA/EACA suggests that the results of randomized trials are compatible with nonrandomized trials.

IS OBSERVATIONAL DATA FATALLY FLAWED?

The controversy continues with the recent publications by Dietrich et al., Schneeweiss et al., and Shaw et al. In the current debate about the apparent discrepancy between randomized and observational comparative trials of aprotinin, the tendency has been to dismiss outright the observational data as fatally flawed. However, risk data from observational studies cannot be rightly dismissed simply on the basis of lack of randomization, as there is strong empirical evidence that observational studies more commonly estimate numerically smaller risks (i.e., more conservative numeric absolute and relative increases) than their corresponding randomized trials. Combining studies through meta-analysis may provide the ability to overcome some limitations of study size; however, randomized trials frequently enroll relatively low risk cohorts and underreport adverse events in their published reports. Observational trials allow the inclusion of a large cohort of patients with varying risk factors in the real world setting and thus may be better suited for studying adverse outcomes. While it is widely known that the best evidence for efficacy come from randomized trials, it is now accepted that the best evidence on harms will often come from large observational studies, particularly when the adverse events are uncommon or require long follow-up for detection.

WILL THE BART TRIAL END THE CONTROVERSY?

The BART trial, a randomized trial with a target sample size of close to 3000 high risk patients, recently halted enrollment because of safety concerns with aprotinin. Preliminary data from the BART trial suggest an increase in the mortality rate in the aprotinin-treated group compared to either the TA or EACA groups. The difference and the trend were not statistically significant but were concerning enough to terminate the trial before enrollment was complete. The lack of statistical significance should not be surprising given outcomes of a similar magnitude as those found in this meta-analysis; the sample size of BART was insufficient to demonstrate statistically significant differences in mortality for AP versus TA/EACA. BART was powered to find absolute differences in the range of 10% (from 50% to 40%) for blood transfusion and is not powered to rule out significant differences for risks in the range of 1% (as found in our meta-analysis).

WHAT ARE THE LIKELY ABSOLUTE DIFFERENCES IN BENEFITS AND RISKS?

If preliminary estimates are accurate in the BART study, for every 1000 patients treated with aprotinin instead of tranexamic acid, there would be an estimated: ~30 to 50 fewer massive bleeding events (including massive transfusion, re-operation for bleeding, or bleeding from chest tubes) [derived from published event rates of BART at interim analysis, and assuming an ARR = 3–5% for massive bleeding events for aprotinin versus tranexamic acid]. ~20 extra

deaths, even *after* the benefit due to reduced bleeding events and transfusions is accounted for [BART trial suggested NNH = 2%, which translates to 20 per 1000].

CONCLUSIONS AND IMPLICATIONS

The results of randomized and observational trials are congruent, and evidence to date shows no proven significant benefit of AP over TA/EACA. Patient exposure to blood transfusion is not reduced by AP when compared with TA/EACA, and the possibility that AP may cause harm including death, stroke, myocardial infarction, or renal failure cannot be ruled out compared with TA/EACA.

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