Putting the record straight on aprotinin as safe and effective: Results from a mixed treatment meta-analysis of trials of aprotinin

Neil Howell, PhD, FRCS(C-Th),[a,b] Eshan Senanayake, MRCS,[a,b] Nick Freemantle, PhD,[c] and Domenico Pagano, MD, FRCS(C-Th)[a,b]

Objective: Meta-analysis of small, randomized, placebo-controlled trials demonstrated efficacy and safety of aprotinin. After highly publicized retrospective studies and the early stopping of the Blood Conservation Using Antifibrinolytics in a Randomized Trial (BART), aprotinin was withdrawn. We conducted a new meta-analysis (including BART) on safety and efficacy of aprotinin in cardiac surgery.

Methods: We conducted a mixed treatment comparisons network meta-analysis estimating the effects of aprotinin and alternative agents in reducing blood loss during surgery. We implemented a combination of direct and indirect evidence in mixed treatment comparisons and estimated relative effects for different agents on all-cause mortality and return to the operating room for bleeding and conducted a supportive analysis of the effects of different agents with only directly randomized trials.

Results: Mixed treatment analysis of 88 trials randomizing 15,528 patients to 1 of 3 antifibrinolytic agents demonstrated no difference in mortality between placebo and antifibrinolytic agents. Analysis of aprotinin versus tranexamic acid and ε-aminocaproic acid in 17 and 6 trials, respectively and tranexamic acid versus ε-aminocaproic acid in 5 trials demonstrated no difference in mortality between treatment allocations. All agents were superior to placebo in reducing reexploration for bleeding, with aprotinin numerically superior: aprotinin odds ratio, 2.6 (95% confidence interval, 1.9-3.7); tranexamic acid odds ratio, 1.79 (1.2-2.9), and ε-aminocaproic acid odds ratio, 2.4 (1.3-6.6).

Conclusions: This mixed treatment comparisons meta-analysis demonstrates no increased mortality risk with aprotinin versus other antifibrinolytic agents. All agents were superior to placebo in reducing reexploration for bleeding after adult cardiac surgery. (J Thorac Cardiovasc Surg 2013;145:234-40)

The age and risk profile of patients undergoing cardiac surgery continue to increase.[1] Such patients are at increased risk for significant postoperative bleeding necessitating transfusion of blood and blood products or further surgical intervention.[2,3] Although modern treatments have resulted in similar early hospital mortalities between those who have significant bleeding problems and those who have not, this complication is still associated with significant resource utilization and could affect adversely late survival after surgery.[3-5] Meta-analyses of antifibrinolytic agents has shown that they reduce the incidence of clinically significant bleeding, reducing both the need for transfusion and the need for surgical reexploration.[6]

Blood transfusion itself is not a hazard-free intervention, with the well-described risks of infectious disease transmission, acute lung injury necessitating prolonged ventilation, perioperative myocardial infarction, and altered immunity. Cardiac surgery accounts for a large proportion of blood transfusion worldwide, almost 10% of all blood transfusions.[7] The importance of blood conservation in cardiac surgery should therefore be considered, and at present the use of antifibrinolytic drugs remains a key part of this strategy.

The serine protease inhibitor aprotinin was a commonly used agent in this strategy, until the Blood Conservation Using Antifibrinolytics in a Randomized Trial (BART) study[8] was terminated early in response to concerns of increased mortality associated with this agent. Since then, agents such as tranexamic acid and ε-aminocaproic acid have now become commonly used in blood conservation strategies in cardiac surgery. These agents have limited safety data and their use is not licensed in most countries.

BART has considerable design limitations, including the lack of placebo control. These limitations have been recently recognized by Health Canada (the department of the government of Canada responsible for the national public health) by reintroducing the use of aprotinin and calling for further safety trials. More recently, the European Medicine Agency has recommended the lifting of the restrictions on the use of aprotinin.[9] We conducted a mixed treatment comparison (MTC) network meta-analysis to estimate the effects of aprotinin and alternative agents in reducing blood

From the Department of Cardiac Surgery[a] and the School of Clinical and Experimental Medicine,[b] University Hospital Birmingham, Birmingham, UK; and the Department of Primary Care and Population Health,[c] University College London, London, UK.

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Address for reprints: Domenico Pagano, MD, FRCS(C-Th), FESC, University Hospital Birmingham, Edgbaston, Birmingham, West Midlands B15 2TT, UK (E-mail: Domenico.pagano@uhb.nhs.uk).

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Abbreviations and Acronyms
BART = Blood Conservation Using Antifibrinolytics in a Randomized Trial
MTC = mixed treatment comparison

loss during surgery and to examine the safety profiles of these agents.[10]

MATERIALS AND METHODS

Trials of aprotinin were identified and data were abstracted from the Cochrane meta-analysis by Henry and colleagues.[7] We conducted an MTC network meta-analysis to estimate the effects of aprotinin and alternative agents in reducing blood loss during surgery.[10] There are two roles for MTC analysis. The first is to strengthen inference concerning the relative efficacies of a pair of treatments by including both "direct" and "indirect" comparisons. The other is to facilitate simultaneous inference regarding all treatments, for example to select the best treatment.[10] MTC and network meta-analysis methods have become widely used in the evaluation of treatments and form an important part of the work of organizations such as the National Institute for Health and Clinical Excellence (NICE; http://www.nicedsu.org.uk/), which actively promotes the use of MTC methods.

We estimated the relative effects for different agents on the outcomes of all-cause mortality and return to the operating room for bleeding. We then conducted a supportive analysis of the effects of different agents with only the directly randomized trials and performed a number of analyses.

The first analysis was an MTC analysis of comparative trials that had an active comparator. The second was an MTC analysis extended to all randomized trials, including all placebo-controlled trials. The third compared the effects of antifibrinolytic agents both with placebo and with each other with respect to return to the operating room for bleeding. The lists of included trials for the analysis of mortality and return to the operating room for bleeding are provided in Tables 1 and 2, respectively.

RESULTS

The first analysis of comparative trials identified 17 trials comparing aprotinin with tranexamic acid, 5 trials comparing tranexamic acid with ε-aminocaproic acid, and 6 trials comparing aprotinin with ε-aminocaproic acid, as shown in Figure 1. The patient numbers for each treatment are shown in Table 3. As shown in Figure 2, no differences in mortality were demonstrated in this 3-way analysis, including comparing aprotinin versus tranexamic acid (odds ratio [OR], 0.83; 95% confidence interval [CI], 0.48-1.83).

The second analysis of patients randomly allocated to treatment or control identified 88 trials. Figure 3 describes the network of these, the majority (54/88) of which were between aprotinin and control. The overall patient numbers analyzed are shown in Table 4, again with the greatest number being randomly allocated to aprotinin (n = 6284). Comparing all 3 agents with each other also demonstrated no differences in mortality between groups, as shown in Figure 4, including aprotinin versus tranexamic acid (OR, 0.73; 95% CI, 0.45-1.21) and aprotinin versus placebo (OR, 1.11; 95% CI, 0.75-1.53).

The third analysis compared the 3 antifibrinolytic agents with each other and with placebo, with respect to the outcome of reexploration for bleeding, as shown in Figure 5. All 3 agents were shown to be superior to placebo in reducing reexploration for bleeding: aprotinin OR, 2.58 (95% CI, 1.91-3.70); tranexamic acid OR, 1.79 (95% CI, 1.22-2.91); and ε-aminocaproic acid OR, 2.4 (95% CI, 1.29-6.59). Aprotinin was shown to be numerically superior to tranexamic acid in reducing reexploration for bleeding, but this result was not statistically significant (aprotinin vs tranexamic acid OR, 1.4; 95% CI, 0.94-2.08).

DISCUSSION

Aprotinin is the most studied antifibrinolytic agent for its use in cardiac surgery, and this MTC meta-analysis, in concordance with previous meta-analyses,[7] supports the contention that it is safe and very effective in preventing reexploration for hemorrhage and blood transfusions. MTC analyses can provide useful estimates of treatment effects, which are derived across a network of interlocking randomized trials. They are particularly useful in the context of inclusion of trials with different comparators, either placebo or active therapies. Our MTC analysis advances the work of Henry and colleagues,[7] who included all relevant trials but used only conventional direct meta-analysis to analyze results. There have been several meta-analyses of randomized trials involving aprotinin. Levi and coworkers in 1999[11] demonstrated that aprotinin was associated with a reduction in mortality (OR, 0.55; 95% CI, 0.34-0.90), a 2001 Cochrane review[12] demonstrated that the use of aprotinin was not associated with increased mortality (OR, 0.87; 95% CI, 0.63-1.9), and the latter finding was confirmed by Sedrakyan and associates[13] in 2004 (OR, 0.96; 95% CI, 0.65-1.4). Furthermore, aprotinin was associated with a reduction in risk of stroke (OR, 0.53; 95% CI, 0.31-0.90) and no increased mortality relative to other antifibrinolytic agents.[13]

Despite these findings, the issue of safety with the use of aprotinin continued to be raised, particularly on the grounds that the majority of the published trials were small, were focused on reduction in blood transfused or reoperation for bleeding, and were not powered to detect a difference in mortality.[14] The meta-analysis of these trials demonstrated significant and clinically important reductions in bleeding and reoperation rate with aprotinin, so a further trial of this agent versus placebo was not considered ethically justified.[15] A further Cochrane review[7] concluded that there were insufficient data to recommend definitively any antifibrinolytic agent rather than another, and with the cost of aprotinin being significantly greater than the other agents, BART was conceived.[8]

BART and Its Aftermath

BART was powered to detect a 50% reduction (from 6% to 3%) in massive bleeding (including reoperation) and a 10% absolute risk reduction in allogeneic exposure to