Institutional report - Cardiac general

Aprotinin increases mortality as compared with tranexamic acid in cardiac surgery: a meta-analysis of randomized head-to-head trials

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Abstract

To determine whether aprotinin increases mortality as compared with tranexamic acid in cardiac surgery, we performed a meta-analysis of randomized head-to-head trials. All prospective randomized head-to-head trials of aprotinin vs. tranexamic acid enrolling patients undergoing cardiac surgery were identified using a web-based search engine (PubMed). For each study, data regarding mortality in both the aprotinin and tranexamic acid groups were used to generate risk ratios (RRs) and 95% confidence intervals (CIs). Study-specific estimates were combined using inverse variance-weighted averages of logarithmic RRs in random-effects models. Our search identified nine trials (eight trials included in the previous meta-analysis and the blood conservation using antifibrinolytics in a randomized trial [BART] study). Seven trials were composed of low-risk patients (n=1291) and two trials consisted of low-risk patients (n=1628). Pooled analysis of the nine trials demonstrated a statistically significant 45% increase in mortality with aprotinin relative to tranexamic acid therapy (RR, 1.45; 95% CI, 1.00–2.65; P=0.05 [0.0499]). The present meta-analysis of updated all randomized head-to-head trials, the best evidence, demonstrated a statistically significant increase in mortality with aprotinin relative to tranexamic acid therapy in cardiac surgery.

Keywords: Aprotinin; Tranexamic acid; Cardiac surgery; Meta-analysis; Randomized head-to-head trial

2. Methods

2.1. Search strategy

All prospective randomized head-to-head trials of aprotinin vs. tranexamic acid enrolling patients undergoing cardiac surgery were identified using a 2-level search strategy: first, a public domain database (MEDLINE) was searched using a web-based search engine (PubMed); second, relevant studies were identified through a manual search of secondary sources including references of initially identified articles and a search of reviews and commentaries. The MEDLINE database was searched from January 1966 to May 2008, and MeSH keywords included aprotinin, tranexamic acid, cardiac surgical procedures, and randomized controlled trial.

2.2. Study selection

Studies considered for inclusion met the following criteria: the design was a prospective randomized controlled clinical trial; the study population was adult patients undergoing cardiac surgery; patients were randomly assigned to aprotinin vs. tranexamic acid therapy; and main outcomes included mortality. We included data published as full-text journal publications.

2.3. Data abstraction

Data regarding detailed inclusion criteria and mortality were abstracted (as available) from each individual study.

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2.4. Statistical analysis

For each study, data regarding mortality in both the aprotinin and tranexamic acid groups were used to generate RRs and 95% CIs. For trials in which either or both of the groups had no event of death, the estimate of treatment effect and its standard error were calculated after adding 0.5 to each cell of the 2×2 table for the trial. Study-specific estimates were combined using inverse variance-weighted averages of logarithmic RRs in both fixed- and random-effects models. Between-study heterogeneity was analyzed by means of standard χ²-tests. Where no significant statistical heterogeneity was identified, the fixed-effect estimate was used preferentially as the summary measure. Publication bias was assessed graphically using a funnel plot and mathematically using an adjusted rank-correlation test, according to the method of Begg and Mazumdar [11]. All analyses were conducted using review manager (RevMan) (Computer program) (Version 5.0) (Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2008) and Microsoft Excel (Version 11.5.0).

3. Results

Our search identified nine prospective randomized head-to-head clinical trials [2–10] of aprotinin vs. tranexamic acid therapy enrolling patients undergoing cardiac surgery. Eight [2–9] of the nine trials (except for the BART [10] study) had been included in the previous meta-analysis [1].

In the BART study [10], patients underwent one of the following high-risk cardiac surgical procedures for which cardiopulmonary bypass (CPB) was required: repeat cardiac surgery, isolated mitral valve replacement, combined valve and coronary artery bypass grafting (CABG), multiple valve replacement or repair, and surgery of the ascending aorta or aortic arch. Patients who required either urgent or elective procedures were considered eligible. The study excluded patients who were undergoing lower risk operations, such as isolated primary CABG with or without CPB, isolated mitral valve repair or aortic valve replacement (AVR). Kuitunen and associates [2] included patients scheduled for elective primary CABG. In the trial by Diprose and colleagues [3], patients were scheduled to receive either CABG or single valve repair or replacement. Patients undergoing emergency surgery and combined or redo surgery were excluded. Casati and co-workers [4] included patients scheduled for primary elective cardiac surgery necessitating CPB. In the trial by Wong et al. [5], patients undergoing elective, high transfusion risk cardiac procedures were studied. The procedures included repeat cardiac operations (CABG or valvular operation), combined procedures (valvular operation plus CABG), and other complex procedures (multiple valve replacement, ascending aortic graft). Nuttall and associates [6] enrolled patients scheduled for elective revision sternotomy for CABG, or cardiac valve surgery, or a combination of the two. In the study by Casati and colleagues [7], patients scheduled for first-time elective cardiac surgery requiring CPB were included. Mongan and co-workers [8] enrolled patients scheduled for elective primary CABG. In the trial by Blauhut et al. [9], a condition requiring emergency surgery or re-operation was excluded.

Pooled analysis of the nine trials (representing 3229 patients) demonstrated a statistically significant 45% increase in mortality with aprotinin relative to tranexamic acid therapy in fixed-effect models (RR, 1.45; 95% CI, 1.00 [1.0002]–2.11; P=0.05 [0.0499]) (Fig. 1). When the four trials [2, 3, 6, 8] reporting no events of death in both the groups were excluded and data from the remaining five trials [4, 5, 7, 9, 10] were pooled using a fixed-effects model (representing 2834 patients), aprotinin therapy was associated with a 47% increase in mortality relative to tranexamic acid therapy that remained statistically significant (RR, 1.47; 95% CI, 1.01–2.15; P=0.05 [0.0464]) (Fig. 2). There was minimal trial heterogeneity and accordingly no difference in the pooled result from random-effects modeling. To assess publication bias we generated a funnel plot of the logarithm of effect size vs. the standard error for each study (Fig. 3). There was no evidence of significant publication bias (P=1.00 by Begg adjusted rank-correlation test).

4. Discussion

The safety of aprotinin was called into question in 2006 and 2007 when the results of an international cohort study, by Mangano and associates [12, 13], of patients undergoing CABG were published. The authors demonstrated increased risks of renal failure, myocardial infarction, and stroke and increased 5-year mortality with aprotinin but not with the lysine analogues. Two additional cohort studies showed in
2008 that patients undergoing CABG who received aprotinin had greater mortality than those who received amino-caproic acid in the short-term as reported by Schneeweiss and colleagues [14] and in the long-term as reported by Shaw and co-workers [15]. The present meta-analysis of updated all randomized head-to-head trials, the best evidence, demonstrated a statistically significant increase in mortality with aprotinin relative to tranexamic acid therapy in cardiac surgery. The previous meta-analysis [1] included seven trials [2–4, 6–9] composed of low-risk patients (representing 1612 patients) and merely one trial [5] consisting of high-risk patients (representing 77 patients). Our updated analysis, which added the BART study [10], included seven trials [2–4, 6–9] composed of low-risk patients (representing 1601 patients) and two trials [5, 10] consisting of high-risk patients (representing 1628 patients). The weight of high-risk trials increased from 4.6% in the previous analysis to 50.4% in the present analysis. Although the BART study itself demonstrated a statistically non-significant increase in mortality with aprotinin relative to tranexamic acid therapy (RR, 1.54; 95% CI, 0.99–2.42) probably due to early termination, adding the trial to a meta-analysis (i.e. increasing the weight of high-risk trials) led the pooled RR for mortality to be statistically significant (RR, 1.45; 95% CI, 1.00 [1.0002]–2.11; P = 0.05 [0.0499]). In the present study we focused on the outcome of death. Although the previous meta-analysis [1] demonstrated that aprotinin reduced total blood loss over tranexamic acid (weighted mean difference, −195 ml; 95% CI, −286 to −105 ml; P < 0.001), a significant increase in the risk of death associated with aprotinin as compared with tranexamic acid, demonstrated by the present meta-analysis, precludes its use in cardiac surgery.

References

than an adverse effect of aprotinin was not statistically significant. As a consequence, the increased relative use of tranexamic acid appeared to reduce mortality; however, this effect hospital stay as compared to 61% in the tranexamic acid group (the aprotinin group 47% of patients received allogeneic blood during the study included 220 patients undergoing primary coronary artery revascularization. N Engl J Med 2006;354:353–365.


eComment: A comparison of the safety of aprotinin and tranexamic acid in cardiac surgery

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It appears that meta-analyses agree that aprotinin increases the risk of death compared to lysine analogues, as you demonstrate in your review [1]. However, this conclusion is not as clear if we consider the clinical events that might cause an increase in the risk of death. Although there was an increase in cardiac death among patients who received aprotinin in the BART study, there was no increase in myocardial infarction, stroke or renal failure either in this trial or in the meta-analyses of Henry et al. [2]. The use of tranexamic acid appeared to reduce mortality; however, this effect was not statistically significant. As a consequence, the increased relative risk of death seen in the indirect comparison of aprotinin and tranexamic acid is because of lower mortality with the use of tranexamic acid, rather than an adverse effect of aprotinin [2].

Notably, Dietrich et al. [3], in a prospective, randomized, double-blind study included 220 patients undergoing primary coronary artery revascularization (CABG) or aortic valve replacement (AVR) demonstrated that: a) in the aprotinin group 47% of patients received allogeneic blood during the hospital stay as compared to 61% in the tranexamic acid group (P = 0.036); b) aprotinin conferred a 23% reduction in allogeneic transfusion risk; c) moreover, the heparin requirement was reduced: 19% of the patients in the aprotinin group and 45% in the tranexamic acid group received at least one additional bolus heparin during cardiopulmonary bypass (P < 0.001); d) troponin T levels postoperatively and on postoperative day 1 were significantly higher in the tranexamic acid group (P = 0.017). Finally, no differences in renal, cardiac, or mortality outcomes were observed. In conclusion, concerning the rate of transfusion of red blood cells, tranexamic acid was slightly inferior in patients undergoing CABG, but there was no difference in patients receiving AVR.

On the other hand, Martin et al. [4], demonstrated that administration of aprotinin should be avoided in coronary artery bypass graft and high-risk patients, whereas administration of tranexamic acid is not recommended in valve surgery analyzing the incidence of acute myocardial infarction, atrial fibrillation or renal dysfunction/failure in corresponding patients.

Finally, Later et al. [5] indicated that aprotinin is the most effective antifibrinolytic agent in patients with normal renal function scheduled for low or intermediate risk cardiac surgery. Especially, aprotinin was about twice as effective as tranexamic acid in reducing total postoperative blood loss (estimated median difference 155 ml, P < 0.001). Accordingly, aprotinin reduced packed red blood cell transfusions more than tranexamic acid, although the difference did not reach statistical significance. Only aprotinin significantly reduced the proportion of transfused patients when compared with placebo (mean difference –20.9%, P = 0.013), and only aprotinin completely abolished bleeding-related re-explorations (mean difference 6.8%, P = 0.004). Neither antifibrinolytic agent increased the incidence of mortality (mean difference tranexamic acid –0.4%, P = 0.79, mean difference aprotinin –1.3%, P = 0.62) compared with placebo.

In conclusion, the choice of aprotinin or tranexamic acid should be based on the type and severity of cardiac surgery and existing co-morbidity.

References


