Tranexamic acid and aprotinin in low- and intermediate-risk cardiac surgery: a non-sponsored, double-blind, randomised, placebo-controlled trial

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Abstract

Objective: Tranexamic acid has been suggested to be as effective as aprotinin in reducing blood loss and transfusion requirements after cardiac surgery. Previous studies directly comparing both antifibrinolytics focus on high-risk cardiac surgery patients only or suffer from methodological problems. We wanted to compare the effectiveness of tranexamic acid versus aprotinin in reducing postoperative blood loss and transfusion requirements in the patient group representing the majority of cardiac surgery patients: low- and intermediate-risk patients.

Methods: We conducted a non-sponsored, double-blind, randomised, placebo-controlled trial in which 298 patients scheduled for low- or intermediate-risk (mean logistic EuroSCORE 4.1) first-time heart surgery with use of cardiopulmonary bypass were randomised to receive either tranexamic acid, high-dose aprotinin, or placebo. All patients had preoperative normal renal function. End points of the study were monitored from the time of surgery until patient discharge. This trial was executed between June 2004 and October 2006.

Results: Both antifibrinolytics significantly reduced blood loss and transfusion requirements when compared with placebo. Aprotinin was about twice as effective as tranexamic acid in reducing total postoperative blood loss (estimated median difference 155 ml, 95% confidence interval (CI) 60—260; \( p < 0.001 \)). 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%, 95% CI 7.3—33.5; \( p = 0.013 \)), and only aprotinin completely abolished bleeding-related re-explorations (mean difference 6.8%, 95% CI 1.6—13.4; \( p = 0.004 \)). Neither antifibrinolytic agent increased the incidence of mortality (mean difference tranexamic acid 0.4%, 95% CI 4.6 to 4.4; \( p = 0.79 \)), mean difference aprotinin 1.3%, 95% CI 6.2 to 3.5; \( p = 0.62 \)) or other serious adverse events when compared with placebo. Conclusion: Aprotinin has clinically significant advantages over tranexamic acid in patients with normal renal function scheduled for low- or intermediate-risk cardiac surgery.

Keywords: Surgical blood loss; Postoperative blood loss; Antifibrinolytic agents; Blood transfusion

1. Introduction

Minimising blood loss and transfusion requirements is of vital importance in cardiac surgery. This has given rise to the widespread use of two classes of antifibrinolytic agents, both proven to abate postoperative bleeding: the lysine analogues (e.g., tranexamic acid) and the serine protease inhibitors (i.e., aprotinin). Although aprotinin seems more effective and has a broader spectrum of effects, its routine use has been hampered by concerns about safety and costs. For this reason, tranexamic acid has been advocated as a commendable alternative, despite discussion on less effectiveness. The question whether or not the use of any antifibrinolytic agent is warranted in patients with low or intermediate operative risk has never been answered: previous studies directly comparing both antifibrinolytics either focus on high-risk patients or suffer from methodological problems, including lack of power, to decide which antifibrinolytic can best be used in patients representing the majority of cardiac surgery patients [1]. We conducted a non-sponsored,
single-centre, double-blind, randomised, placebo-controlled trial to evaluate the efficacy of tranexamic acid and aprotinin in reducing both postoperative blood loss and transfusion requirements in low- and intermediate-risk patients with normal renal function. Clinically important secondary outcomes were in-hospital mortality, morbidity, and length of intensive care and hospital stay.

2. Materials and methods

2.1. Trial design

Patients were randomised to receive either tranexamic acid (Cyklokapron®, Pfizer Inc., USA) according to a full dose regime [2] (1 g loading dose, 500 mg added to the cardiopulmonary bypass (CPB) system prime, and a continuous infusion of 400 mg/h), high-dose aprotinin (Trasylo® (Bayer AG Germany) according to the Hammersmith protocol (2 x 10^6 KIU aprotinin loading dose, 2 x 10^6 KIU added to the CPB system prime, and a continuous infusion of 5 x 10^5 KIU/h during CPB), or placebo (0.9% saline solution) according to an identical regime. Sample size was calculated using surveillance data on blood loss and transfusion requirements from both surveillance studies performed in our institution and in the available literature [3]. Aspirin a 50% reduction in postoperative blood loss, a sample size of 100 patients per group was calculated to have an 80% power to demonstrate a difference with a p value of 0.05, using a two-sided test. The aimed total sample size was thus 300 patients. The trial protocol was approved by the internal review board of the Leiden University Medical Centre (LUMC) under protocol number PO3.130, and funded by intramural sources only. This trial has been registered at the Dutch Trial Register, ISRCTN00157697, and has been reported in accordance with the Consort Statement 2001 checklist.

2.2. Setting

The LUMC is a quaternary-care university hospital, employing nine surgeons qualified for the full range of adult cardiac surgery operations during the trial period.

2.3. Trial participants

From June 2004 to October 2006, all adult patients admitted to the department of cardiothoracic surgery were screened for eligibility, inclusion criteria being patients selected for first-time, non-complex (one or two procedures) heart surgery with the use of CPB. Patients with previous sternotomy, known bleeding disorders, an abnormal preoperative coagulation profile for reasons other than anticoagulant therapy, or treatment with antiplatelet agents within 5 days before surgery were excluded. Other exclusion criteria were known or suspected allergy to aprotinin, plasma creatinine concentration >1.36 mg/dl (120 μmol/l), pregnancy, a history of thrombosis, or an emergency operation. Patients were included the day before surgery once informed consent was obtained.

2.4. Trial organisation and procedure

Before the start of the trial, an independent statistician prepared sequentially numbered opaque envelopes containing a prescription for the trial medication using a computer-generated randomisation list. When inclusion criteria were met, patients received information on the trial outline during their first visit to the outpatient clinic and again on the day before surgery. The next available envelope was allocated by the researcher responsible for seeing candidate patients once informed consent was obtained. An independent anaesthesia assistant then prepared the trial medication overnight in identically appearing syringes labelled with the patients’ trial number only. Inclusion criteria were checked once more before surgery was started. All caretakers were blinded to medication allocation. Randomisation codes were only revealed to the researchers once recruitment, data collection, and laboratory analyses were complete.

2.5. Operative procedure and intensive care unit management

To rule out hypersensitivity to aprotinin, a 1 ml test dose of the trial medication was used 10 min before the initial loading dose was administered. All patients received standard anaesthetic procedures. A heparin loading dose was administered before start of CPB to achieve a kaolin activated coagulation time (ACT junior®) >480 s during bypass. Blood temperature was kept between 35 °C and 37 °C, and myocardial protection was achieved by intermittent antegrade warm blood cardioplegia. At the end of CPB, heparin was reversed using protamine sulphate in a ratio of 1:1. Neutralisation was considered adequate when the activated clotting time had returned within 10% of the pre-heparin value. Before heparinisation and after reversal with protamine, blood from the operative field was retrieved in a cell-saver device (Compact-Advanced, Dideco®) but was only washed and returned to the patient if blood loss exceeded 500 ml. Transfusion criteria for packed red blood cell (PRBC) transfusions were: haemoglobin level <6.4 g/dl during CPB, <8.1 g/dl after cessation of CPB, and <8.7 g/dl when blood loss in the intensive care unit (ICU) exceeded 200 ml/h. All PRBC units were leucocyte depleted. Platelets were transfused when platelet count was <50 x 10^9/l, or <100 x 10^9/l when blood loss exceeded 200 ml/h. Fresh frozen plasma (FFP) was administered when the activated partial thromboplastin time and prothrombin time were prolonged during active bleeding. Fluid therapy in the ICU consisted of glucose/NaCl 0.9% infusion (2.0 l/24 h). Additional fluids were administered when deemed necessary by the attending physician.

2.6. Measures and definitions

All intra- and postoperative measurements were performed by caretakers not involved in the trial and blinded to group assignment. Intraoperative blood loss was not included in the original trial protocol and retrieved later from the patients’ medical records.
2.6.1. Primary end points

Primary end points were total postoperative blood loss and transfusions requirements. Mediastinal chest tube blood loss was measured every hour after arrival at the ICU. Mediastinal shed blood was not reinfused. Transfusion requirements were defined as total PRBC, total FFP, and total platelet transfusions as well as the proportions of patients requiring PRBC, FFP, and total platelet transfusions and the proportion of patients requiring any blood product transfusion. In case of a re-exploration, assessment of transfusion requirements and mediastinal shed blood was continued and not stopped. The number of blood products transfused was checked against the blood bank’s records.

2.6.2. Secondary end points

Secondary end points included in-hospital mortality, re-exploration, perioperative myocardial infarction, intra-aortic balloon pump (IABP) use, mediastinitis, renal failure and use of continuous venovenous haemofiltration (CVVH), neurological complications, sepsis, postoperative intubation time, and length of ICU and hospital stay. Surgical re-exploration was considered if bleeding >400 ml/h for 2 h, >300 ml/h for 3 h, >200 ml/h for 4 h, or exceeded 1000 ml in total postoperatively. Perioperative myocardial infarction required (1) new Q-waves or new, persistent ST-segment or T-wave changes in the ECG recording, and (2) a significant rise in troponin-T levels (>1.0 ng/ml in case of coronary artery bypass grafting and >2.0 ng/ml when valvular surgery was performed). Kidney function was assessed in the first 48 h postoperatively. Renal failure as defined by Mangano et al. [4] required a postoperative serum creatinine of at least 2.0 mg/dl with an increase over the preoperative baseline level of at least 0.7 mg/dl. The RIFLE classification for acute renal failure was used for further assessment of postoperative kidney function: risk of renal dysfunction was defined as a 1.5 times increase in perioperative creatinine plasma concentration or a urine output <0.5 ml/kg/h in 6 h. Kidney injury was defined as a 2 times increase in perioperative creatinine plasma concentration or a urine output <0.5 ml/kg/h in 12 h, whilst renal failure was defined as a 3 times increase in perioperative creatinine plasma concentration or a urine output <0.3 ml/kg/h in 24 h [5]. Neurological complications included delirium, clinically diagnosed stroke, and encephalopathy. In concordance with another study in our institution evaluating the incidence of multiple organ failure (MOF) and the systemic inflammatory response syndrome (SIRS), incidence of MOF and SIRS were evaluated in 233 and 206 consecutive patients, respectively, using the MOF criteria by Knaus et al. [6] and the SIRS criteria proposed by the American College of Chest Physicians. Length of ICU and hospital stay was defined as the number of days between the date of surgery and the date of ICU and hospital discharge, respectively.

3. Cost analysis

A simple cost analysis evaluated costs directly influenced by the use of antifibrinolytics: the costs of the antifibrinolytics, all blood product transfusions, use of cell-saving equipment, re-explorations, and the per diem charges for the ICU and ward.

3.1. Monitoring

During the trial period, two publications based on observational studies addressed serious concerns regarding the safety of aprotinin in cardiac surgery [4,7]. It was decided to stop patient inclusion after the publication of results of the first study. An independent statistician, medical doctor, and researcher were asked to perform a safety analysis using the preliminary data of the 207 patients included in the trial by that time. No significant differences in incidence of adverse events between the trial groups were found warranting immediate abortion of the trial. The patient information letter was adapted and the internal review board was asked for approval to restart the trial. After 2 weeks, inclusion was continued. The second paper was published when the trial was nearly completed.

3.2. Statistical approach

Statistical analysis was performed using SPSS software, version 14.0.2 (SPSS Inc., Chicago, IL). For continuous variables, differences between the three trial groups were tested by one-way analysis of variance or the Kruskal–Wallis test, where appropriate. Post-hoc analysis for pairwise group comparisons was performed using the Tukey and Mann–Whitney U test, respectively. In the Mann–Whitney U test, the problem of multiple comparisons was addressed by the Benjamini–Hochberg correction. For categorical variables, differences between the groups were tested by the chi-square test. The likelihood ratio test statistic was used when the assumption of minimal expected cell frequency was violated. Ninety-five percent confidence intervals were calculated using Confidence Interval Analysis software, version 2.1.2 (University of Southampton, Southampton, UK). A p value <0.05 was considered statistically significant, using a two-sided test.

4. Results

Of the 333 patients enrolled, 298 were eligible for data analysis (Fig. 1). In 21 patients scheduled for on-pump surgery, it was perioperatively decided not to use CPB. This decision depended on accessibility of distal coronaries.

4.1. Demographic and preoperative clinical data

No statistically significant differences in baseline characteristics were found between the three trial groups (Table 1), except for preoperative β-blocker use, which was significantly less in the tranexamic acid group when compared with the aprotinin (p = 0.029) and placebo (p = 0.017) groups.

4.2. Primary end points

Both tranexamic acid and aprotinin significantly reduced total postoperative blood loss and total PRBC transfusions...
when compared with placebo (Table 2). When comparing both antifibrinolytics with one another, aprotinin was significantly more effective in reducing postoperative blood loss, whilst the difference in reducing total PRBC transfusions was not significant ($p = 0.074$). Although reduction of total FFP transfusions was seen in both medication groups this reduction did not reach statistical significance when compared with placebo. The same held for total platelet transfusions.

Only aprotinin significantly decreased the proportion of patients that received a PRBC transfusion when compared with placebo (Fig. 2). The number needed to treat (NNT) to prevent any PRBC transfusion during hospital stay was 4.8 (95% CI 3.0—13.7) for aprotinin versus 7.5 (95% CI 3.9—1054.9) for tranexamic acid. The proportion of patients without any blood product transfusion was significantly higher in the aprotinin group versus the placebo group.

4.3. Secondary end points

The incidence of postoperative complications is shown in Table 3. The overall rate of postoperative re-explorations was lower in the aprotinin group when compared with tranexamic acid and placebo. When causes for re-exploration
were restricted to 'non-surgical bleeding' and 'late tamponade', aprotinin treated patients had significantly less re-explorations than placebo (mean difference 6.8%, 95% CI 1.6—13.4; \( p = 0.032 \)) or tranexamic acid treated patients (mean difference 8.1%, 95% CI 2.6—15.1; \( p = 0.017 \)), the latter having almost similar rates.

The incidence of perioperative myocardial infarction was significantly reduced in both the aprotinin (mean difference

Table 2: Transfusion related variables.

<table>
<thead>
<tr>
<th>Variable</th>
<th>PL(^a) (n = 103)</th>
<th>TX(^b) (n = 99)</th>
<th>AP(^c) (n = 96)</th>
<th>PL versus TX</th>
<th>PL versus AP</th>
<th>TX versus AP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cell-saver use</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Incidence (%)</td>
<td>53 (51.4)</td>
<td>55 (55.5)</td>
<td>36 (37.5)</td>
<td>-4.1%</td>
<td>14.0%</td>
<td>18.1%</td>
</tr>
<tr>
<td>Difference(^d)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>95% CI</td>
<td>-17.5 to 9.5</td>
<td>0.2—27.0</td>
<td>4.1—31.1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>( p ) value</td>
<td>0.56</td>
<td>0.040</td>
<td>0.010</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total MCTD loss(^b) (ml)</td>
<td>860 (740)</td>
<td>760 (540)</td>
<td>546 (405)</td>
<td>130</td>
<td>295</td>
<td>155</td>
</tr>
<tr>
<td>Median (inter quartile range)</td>
<td>10—260</td>
<td>185—410</td>
<td>60—260</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Estimated difference</td>
<td></td>
<td></td>
<td></td>
<td>0.034</td>
<td>&lt;0.001</td>
<td>0.002</td>
</tr>
<tr>
<td>95% CI</td>
<td></td>
<td></td>
<td></td>
<td>0.0—0.0</td>
<td>0.0</td>
<td>0.001</td>
</tr>
<tr>
<td>( p ) value(^d)</td>
<td>0.038</td>
<td>&lt;0.001</td>
<td>0.004</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total units PRBC(^c) transfused,</td>
<td>2.0 (3.0)</td>
<td>1.0 (2.0)</td>
<td>0.5 (1.0)</td>
<td>0.0</td>
<td>1.0</td>
<td>0.0</td>
</tr>
<tr>
<td>Median (inter quartile range)</td>
<td></td>
<td></td>
<td></td>
<td>0.0—1.0</td>
<td>0.0—1.0</td>
<td>0.0—1.0</td>
</tr>
<tr>
<td>Estimated difference</td>
<td></td>
<td></td>
<td></td>
<td>0.038</td>
<td>&lt;0.001</td>
<td>0.074</td>
</tr>
<tr>
<td>95% CI</td>
<td>0.0—1.0</td>
<td>0.0—1.0</td>
<td>0.0—1.0</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>( p ) value(^d)</td>
<td>0.038</td>
<td>&lt;0.001</td>
<td>0.074</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No PRBC transfused</td>
<td>30 (29.1)</td>
<td>42 (42.4)</td>
<td>48 (50.0)</td>
<td>13.3%</td>
<td>20.9%</td>
<td>7.6%</td>
</tr>
<tr>
<td>Incidence (%)</td>
<td></td>
<td></td>
<td></td>
<td>0.1—25.9</td>
<td>7.3—33.5</td>
<td>-6.3 to 21.1</td>
</tr>
<tr>
<td>Difference(^d)</td>
<td></td>
<td></td>
<td></td>
<td>0.057</td>
<td>0.004</td>
<td>0.316</td>
</tr>
<tr>
<td>95% CI</td>
<td>0.1—25.9</td>
<td>7.3—33.5</td>
<td>-6.3 to 21.1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>( p ) value</td>
<td>0.057</td>
<td>0.004</td>
<td>0.316</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No blood products transfused</td>
<td>22 (21.4)</td>
<td>30 (30.3)</td>
<td>37 (38.5)</td>
<td>8.9%</td>
<td>17.2%</td>
<td>8.2%</td>
</tr>
<tr>
<td>Incidence (%)</td>
<td></td>
<td></td>
<td></td>
<td>-3.1 to 20.8</td>
<td>4.5—29.3</td>
<td>-5.0 to 21.2</td>
</tr>
<tr>
<td>Difference(^d)</td>
<td></td>
<td></td>
<td></td>
<td>0.152</td>
<td>0.009</td>
<td>0.232</td>
</tr>
<tr>
<td>95% CI</td>
<td>-3.1 to 20.8</td>
<td>4.5—29.3</td>
<td>-5.0 to 21.2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>( p ) value</td>
<td>0.152</td>
<td>0.009</td>
<td>0.232</td>
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</tbody>
</table>

\(^a\) PL: placebo, TX: tranexamic acid, AP: aprotinin.

\(^b\) MCTD loss: mediastinal chest tube drain loss.

\(^c\) PRBC: packed red blood cells.

\(^d\) The Kruskal—Wallis test was used here. The \( p \) values have been corrected for multiple testing using the Benjamini—Hochberg correction.
6.7%, 95% CI 0.8—13.6; \( p = 0.023 \)) and tranexamic acid group (7.8%, 95% CI 2.5—14.6; \( p = 0.004 \)) when compared with placebo, with no significant difference between both medication groups.

The incidence of renal failure in the first postoperative 48 h as defined by Mangano et al. [4] was not found to be different for the three trial groups. According to the RIFLE classification, a significant decrease in incidence of the classification ‘risk’ was found in the aprotinin group when compared with placebo (mean difference 8.6%, 95% CI 1.6—16.2; \( p = 0.011 \)). No significant between-group differences were found for the classifications ‘injury’ and ‘failure’.

No differences in incidence of mortality, SIRS, MOF, or length of ICU or hospital stay were found between the three trial groups.

### 4.4. Cost analysis

The simple cost analysis evaluating costs directly affected by the use of antifibrinolytics showed no significant differences between the three trial groups (Table 3).

### 5. Discussion

Aprotinin was superior to tranexamic acid in reducing postoperative blood loss and bleeding-related re-explorations and was the only antifibrinolytic agent that significantly decreased the number of patients that required any blood transfusion. The superiority of aprotinin above tranexamic acid was not reflected by the reduction of PRBC transfusions.
both antifibrinolytics significantly reduced total PRBC transfusions when compared with placebo, but the difference between aprotinin and tranexamic acid did not reach statistical significance.

A closer look at the efficacy data reveals that the reduction in total PRBC transfusions achieved by aprotinin (48.0%) corresponded with its reduction in postoperative blood loss (39.4%). On the other hand, tranexamic acid’s reduction in PRBC transfusions (32.0%) can hardly be explained by its reduction in blood loss (14.5%). Post-hoc analysis of intraoperative blood loss in 205 patients yielded significant reductions in both the tranexamic acid group (estimated median difference 130 ml, 95% CI 18—255; \( p = 0.021 \)) and the aprotinin group (estimated median difference 150 ml, 95% CI 40—255; \( p = 0.007 \)) when compared with placebo (Table 2). In addition, the threshold for using an intraoperative cell-saver device was reached significantly less often in the aprotinin treated patients when compared with both the placebo and tranexamic acid treated patients. We hypothesise that this higher rate of intraoperative cell salvage in the placebo and tranexamic acid groups masked aprotinin’s ability to reduce postoperative transfusions. In fact, converting the amount of cell-saver blood returned into red blood cell transfusions of 270 ml renders the reduction in total red blood cell transfusions achieved by aprotinin (41.6%) and tranexamic acid (17.6%) much more in parallel with the reduction observed in total postoperative blood loss.

Our results, showing aprotinin to be significantly more effective than tranexamic acid in reducing blood loss and the proportion of transfused patients, confirm the findings of several smaller trials. A total of 16 randomised controlled trials involving 4767 patients undergoing various cardiac procedures directly compared high-dose aprotinin with tranexamic acid so far [2,3,9—22]. Four studies identified aprotinin as most potent in reducing blood loss or transfusion requirements [3,11,15,19], whilst none recognised tranexamic acid as superior to aprotinin. Only 2 out of these 16 trials, including 158 patients, used a double-blind, placebo-controlled design; whilst Jamieson et al. (\( n = 101 \), pooled results from two trials) reported that aprotinin and tranexamic acid are equally effective in reducing blood loss in patients undergoing reoperative cardiac valvular surgery, Diprose et al. (\( n = 57 \)) concluded that aprotinin is superior to tranexamic acid in the reduction of patient exposure to any allogeneic transfusion when used in addition to intraoperative cell salvage. The question which antifibrinolytic is most effective in cardiac surgery has been subject of meta-analyses [1,23] and reviews [24,25] too, all based mostly on the outcomes of the above-mentioned 16 trials. Since most of these trials suffer from methodological problems, do not study identical clinical outcomes, and because of heterogeneity of effect size among these trials, the majority of these meta-analyses and reviews could not reach a definite verdict. Furthermore, their results cannot easily be translated to low- and intermediate-risk cardiac surgery patients, the patient group focused on in our trial. Indeed, drug-related safety concerns and costs hamper the routine use of antifibrinolytics and the question whether or not their use in low- and intermediate-risk patients is warranted was never addressed.

As in most efficacy trials, this trial was neither designed nor powered to evaluate low frequency drug-related morbidities. However, based on the results of three observational studies [4,7,8], possible side effects should have been detectable with our sample size. For instance, Mangano et al. found an incidence of myocardial damage of 16% and of renal dysfunction of 8% in aprotinin treated patients. Our data indicate that patients treated with aprotinin or tranexamic acid had a lower incidence of myocardial infarction than placebo treated patients, possibly due to either the reduction in blood loss and transfusion products administered, or to an incidental higher myocardial infarction rate in the placebo group. Patients treated with aprotinin or tranexamic acid had no higher incidence of renal failure. This suggests that the complications seen in the observational studies might be explained by the inclusion of patients at high-risk for developing these. Such patients were excluded in our trial since we focused on low- and intermediate-risk cardiac surgery patients with normal renal function.

A recent trial comparing the effect of aprotinin with tranexamic acid, the BART trial by Furgesson et al. [9], only focused on patients undergoing high-risk cardiac surgery. Besides finding, as we did, that aprotinin is more effective in reducing both the need for blood products and the occurrence of massive bleeding, Furgesson et al. reported a relative 30-day mortality risk of 1.55 (95% CI 1.06—2.22) in the aprotinin group when compared with tranexamic acid treated patients. Although not confirmed by autopsy, the proportion of patients who died of a cardiac cause was higher in the aprotinin group. The investigators concluded that aprotinin should no longer be used in high-risk cardiac surgery. It has to be emphasised that, in comparison to our trial, patients in the BART were older, had a higher incidence of poor or moderate left ventricular function and need for urgent surgery, and a higher body mass index and incidence of diabetes. Furthermore, the BART trial included patients with a history of thromboembolism, preoperative chronic renal dysfunction, and patients scheduled for high-risk repeat and/ or emergency surgery, including surgery of the ascending aorta or aortic arch; all these patients were excluded in our trial.

Fig. 2. Distribution of PRBC transfusions per trial group. PRBC: packed red blood cells. One unit contains 270 ml leucocyte depleted red blood cells.
6. Limitations

This trial has several limitations. First, being also its strength, our results apply to patients with low- or intermediate-risk surgery and normal renal function only. We did choose not to randomise high-risk patients to a placebo group since our standard care was to treat these patients with either aprotinin or tranexamic acid.

Secondly, finding no difference in median PRBC transfusions between both antifibrinolytics might be explained by statistical limitations: the statistical tests for differences in the number of transfusions were hampered by skewed data due to a large number of patients without any transfusion. Therefore, the results of the between-group comparison for the proportion of non-transfused patients might be considered as more reliable. In addition, finding no difference might be explained by underpowering of this trial.

Thirdly, we noticed that the mere monitoring of blood transfusions reduced the overall blood loss and transfusion rate, an effect earlier described for this kind of interventional trials. Transfusion data are influenced by trigger levels, local policies, and the use of intraoperative cell-saving devices. As demonstrated above, avoidance of cell-saving techniques would have resulted in a much larger and possibly statistical significant difference in transfusion reduction between the two drugs.

Lastly, the effect of antifibrinolytics on intraoperative blood loss could not be evaluated as accurate as the effect on postoperative blood loss and therefore only be estimated by analysis of the available data on suction blood loss, cell-saver usage, and blood loss in gauges.

The major strength of our study lies in the non-sponsored, double-blind, randomised, placebo-controlled design and the study group chosen. A total of 298 patients scheduled for low- or intermediate-risk cardiac surgery could be evaluated, representing an estimated 60% of the patients operated upon in a quaternary-care centre and 80% of the patient population in a tertiary-care centre. Our results are therefore likely to be representative of what happens in usual clinical practice and applicable to the majority of cardiac surgery patients for whom the optimal treatment with antifibrinolytics had not previously been established. We can now conclude that aprotinin is the most effective antifibrinolytic agent in this patient group, without increasing costs. In the light of recent publications and the serious concerns about the safety of aprotinin in cardiac surgery, however, tranexamic acid might be regarded as a reasonable alternative.

References


