Redo Cardiac Surgery: Bleeding Control


Cardiac Surgery Department, Mohammed V Military Hospital, Mohammed V University, Rabat, Morocco

Email: *anissdr@yahoo.fr

Abstract

Redo cardiac surgery increases mortality and morbidity. The aim of this study was to determine if aprotinin was superior to tranexamic acid concerning control bleeding loss after redo valve surgery. A retrospective study was conducted from January 1994 until December 2014. 221 patients underwent redo cardiac valve surgery and separated into two groups: aprotinin group (n = 85) and tranexamic acid group (n = 136). Univariate tests were applied for data analysis. A total of 221 patients were enrolled in this study. This cohort was separated into two groups: aprotinin group (n = 85) and tranexamic acid group (n = 136). Euroscore in tranexamic acid group was higher: 5.96 ± 3.04 vs. 5.17 ± 2.83 in aprotinin group (p = 0.055). There was no statistical difference in postoperative mortality between the two groups (p = 0.153). No statistical differences were reported concerning: total blood loss (p = 0.51), red blood cells transfusion (p = 0.215), reexploration for bleeding (p = 0.537) and postoperative renal failure (p = 0.79). There were statistical differences concerning mechanical ventilation time, which is longer in tranexamic acid group (p = 0.008) and the use of inotropic drug support, which is more frequent in the tranexamic acid group (p = 0.001). Our results demonstrated that tranexamic acid and aprotinin reduce transfusion requirement and blood loss. Due to financial reason, we chose tranexamic acid in preventing blood loss in redo valve surgery.

Keywords

Cardiac Surgery, Aprotinin, Tranexamic Acid, Cardiopulmonary Bypass

1. Introduction

Redo cardiac surgery increases mortality and morbidity. Excessive perioperative bleeding is a common complication with over 50% of patients receiving blood
product transfusions [1] [2] [3] [4].

The risk of postoperative morbidity and mortality was increased by perioperative transfusion [5]. Thus, postoperative hemorrhages affect patients’ outcomes, and increase healthcare costs.

Bridges et al. found that re-exploration for control of bleeding after cardiac surgery increased four-fold mortality and sternal infection [6].

In cardiac surgery, bleeding is due to hemostasis changes by exposing blood to CPB circuit and also due to the surgical procedure.

In redo valve surgery, extensive surgical dissection of mediastinal and pleuro-pericardial adherences in order to mobilize the entire heart and facilitate the exposure causes diffuse capillary injuries and tissue damage that increase bleeding.

Cardiopulmonary bypass (CPB) adds major insult to the injury and creates excessive activation of the fibrinolytic system that leads to a bleeding tendency [7].

Therefore, different pharmacologic strategies have been recommended to reduce perioperative blood loss including correction of coagulopathy using tropical agents for example, spraying fibrin sealant over the pericardial surface. But the prophylactic utilization of the intravenous antifibrinolytic agents is the popular approach in preventing blood loss.

In clinical practice, aprotinin, a natural serine protease inhibitor and two lysine analogues tranexamic acid (TXA) and aminocaproic acid [8] have been used to reduce blood loss after cardiac surgery. However, there is still confusion and controversy about the best antifibrinolytic agent.

The aim of this study was to determine if aprotinin was superior to tranexamic acid concerning control bleeding loss after redo valve surgery.

2. Methods

After institutional ethical committee approval, database of all adult patients (≥18 years) were collected retrospectively. All patients who underwent redo cardiac surgery with cardiopulmonary bypass from January 1994 until December 2014 at our institution were included in the present retrospective observational study.

Categories in this database included patients characteristics, comorbidities, operative data, antifibrinolytic agent given, cardiopulmonary bypass time, cross clamp time, blood products transfused, 24 hours chest tube drainage and postoperative complications.

Anesthesia:
All patients were premedicated with 0.1 mg/kg of diazepam. After the transfer to the operating room the patient was given total intravenous anesthesia. This consists of sufentanil 0.5 mg/kg, midazolam 3 - 5 mg/kg, propofol 1 mg/kg, vecuronium 0.6 mg/kg. Antibiotic prophylaxis was given intravenously after induction of anesthesia and before skin incision closure, and continued every 6 hours during 24 hours. Cephazolin combined with aminozid were the standard choice.

Cardiopulmonary bypass:
All patients underwent redo cardiac surgery via median sternotomy.
For anticoagulation, we administered heparin 300 iu/kg intravenously until an activated clotting time (ACT) of >400 s was achieved. All CPB procedures were performed with membrane oxygenator, roller pump and under moderate hypothermia (32˚ - 34˚).

Continuous blood flow was kept between 2.2 and 3 l/min/m². Myocardial protection was achieved by cold high potassium crystalloid cardioplegia solution (St Thomas) before 2000, but after this date, we routinely used cold blood cardioplegia for all patients.

Patients were weaned from CPB when rectal temperature was estimated 36˚C. Before giving protamine, blood from CPB circuit was returned back to patient. Heparin was reversed with protamin sulfate in 1:1 fashion.

Patients were divided into two groups based on the antifibrinolytic agent they were given.

The first group received aprotinin (n = 85). After heparinization, we infused 500,000 kiu before and after protamine administration.

The second group received tranexamic acid (n = 136). When heparinization was done, we injected 15 mg/kg before and after protamine administration.

We evaluated in this study: blood loss were assessed at 6 and 24 hours, hemoglobin level, platelet count and fibrinogen level. Transfusion of blood product was also evaluated.

Adverse events were predefined as follows: low cardiac output syndrome (LOS), postoperative myocardial infarction, renal failure, cerebrovascular event, reexploration due to hemorrhage and reintubation.

30 days mortality was defined as all death during 30 days after surgery.

We recorded these operation’s parameters: type of intervention done, urgency of operation, operation time, CPB time, cross clamping time, time of mechanical ventilation, intensive care unit (ICU) stay, postoperative length of stay and use of inotropic drugs.

Exclusion criteria were as follows: allergy to tranexamic acid or aprotinin, preoperative coagulation defects, preoperative renal failure with hemodialysis.

Data analysis:

Statistical analysis was performed using SPSS 19.0 software (SPSS Inc., Chicago, IL, USA).

Data were represented as mean ± (SD) when the variables were normally distributed or as median with inter-quartile range (IQR) when the variables were not normally distributed.

T-test was used to compare normally distributed data. A non parametric test Mann-Whitney for abnormally distributed variables. A chi-square test $X^2$ or Fisher’s exact test was used to compare ordinal and categorical data respectively.

A p value of less than 0.05 was considered as statistically significant.

3. Results

A total of 221 patients were enrolled in this study. This cohort was divided into
two groups: aprotinin group (n = 85) and TXA group (n = 136).

The patient demographic data are outlined in Table 1. Patients in TXA group were more female (75% vs. 52.9% p = 0.001) and were older (45.81 ± 10.62 years vs. 39.86 ± 9.25 years p = 0.0001) and a higher proportion of them were more symptomatic NYHA functional class III-IV: 68.3% vs. 54.1% p = 0.033. That was explained by the delay of surgery. Duration between the first surgical procedure and the reoperation: 14.69 ± 8 years in TXA group vs. 12.05 ± 5.76 in aprotinin group p = 0.005.

Additionally, the TXA group was in higher preoperative risk score. Euroscore: 5.96 ± 3.04 in TXA group vs. 5.17 ± 2.83 in aprotinin group p = 0.055.

Concerning the rest of demographic data, there were no significant statistically differences between the two groups.

There were no differences in preoperative laboratory parameters between groups.

Preoperative hemoglobin, platelet, fibrinogen, prothrombin time, creatinine levels were similar between groups.

Table 2 shows the reasons of reoperation for patients. Although patients

**Table 1.** Demographics of patients.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Group previous Aprotinin</th>
<th>Group re-sternotomy Tranexamic acid</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>39.86 ± 9.25</td>
<td>45.81 ± 10.62</td>
<td>0.000</td>
</tr>
<tr>
<td>Male/female</td>
<td>40/45</td>
<td>34/102</td>
<td>0.001</td>
</tr>
<tr>
<td>DM (%)</td>
<td>2.35</td>
<td>8.82</td>
<td>0.055</td>
</tr>
<tr>
<td>AH (%)</td>
<td>1.17</td>
<td>5.88</td>
<td>0.158</td>
</tr>
<tr>
<td>Smoking (%)</td>
<td>14.11</td>
<td>9.55</td>
<td>0.298</td>
</tr>
<tr>
<td>Time (years)</td>
<td>12.05 ± 5.76</td>
<td>14.69 ± 8.00</td>
<td>0.005</td>
</tr>
<tr>
<td>NYHA III-IV (%)</td>
<td>54.1</td>
<td>68.3</td>
<td>0.033</td>
</tr>
<tr>
<td>CTR</td>
<td>0.58 ± 0.07</td>
<td>0.59 ± 0.07</td>
<td>0.374</td>
</tr>
<tr>
<td>Previous stroke</td>
<td>4.70</td>
<td>7.35</td>
<td>0.432</td>
</tr>
<tr>
<td>Preoperative RF (%)</td>
<td>4.70</td>
<td>4.41</td>
<td>1</td>
</tr>
<tr>
<td>AF</td>
<td>67.05</td>
<td>71.32</td>
<td>0.502</td>
</tr>
<tr>
<td>Anemia</td>
<td>24.69</td>
<td>35.83</td>
<td>0.095</td>
</tr>
<tr>
<td>LVEF</td>
<td>59.75 ± 10.52</td>
<td>59.51 ± 9.79</td>
<td>0.869</td>
</tr>
<tr>
<td>SPAP (mmHg)</td>
<td>48.63 ± 22.29</td>
<td>51.03 ± 17.94</td>
<td>0.448</td>
</tr>
<tr>
<td>Hemoglobin level</td>
<td>13.70 ± 2.47</td>
<td>12.49 ± 1.83</td>
<td>0.000</td>
</tr>
<tr>
<td>Creatinine</td>
<td>9.70 ± 2.90</td>
<td>9.12 ± 5.10</td>
<td>0.438</td>
</tr>
<tr>
<td>Eurosore</td>
<td>5.17 ± 2.83</td>
<td>5.96 ± 3.04</td>
<td>0.055</td>
</tr>
<tr>
<td>LVEF ≤ 40%</td>
<td>5.88</td>
<td>5.88</td>
<td>1</td>
</tr>
</tbody>
</table>

treated with aprotinin had slightly more closed mitral commissurotomy than patients treated with TXA (55.3% vs. 41.5% p = 0.05), but this difference was of low clinical importance.

Other causes of redo valve surgery were similar between groups.

Intraoperatively (Table 3), patients receiving TXA drug had significantly longer CPB time, aortic cross clamp time, duration of surgical procedure, mechanical ventilation time, ICU stay (p = 0.0001, p = 0.0001, p = 0.0001, p = 0.005 and p = 0.0001) respectively. However, the mean postoperative length of stay was similar between groups: 13.93 ± 6.9 days vs. 13.86 ± 13.82 days (p = 0.97).

The frequency of low cardiac output syndrome was higher in TXA group compared with aprotinin group, but it did not reach statistically significance (18.38% vs. 9.41% p = 0.069). More patients in TXA group were receiving inotropic drugs compared to those treated with aprotinin: 29.41% vs. 10.58% (p = 0.001). Postoperative morbidities between patients treated with tranexamic acid and those treated with aprotinin did not found significant differences (myocardial infarction, renal failure, infection neurological events).

The incidence of excessive blood loss (>1000 ml/24h) was similar in both groups (aprotinin: 7.05% vs. TXA 7.35% p = 0.935).

At six and 24 hours the volume of blood loss was the same between both groups. Patients treated with aprotinin required more transfusion than patient in the tranexamic group, but it didn’t reach statistical significance (45.88% vs. 37.4% p = 0.215).

The need for re-exploration for bleeding was slightly higher in TXA group but without clinical importance (p = 0.537).

The mean level of hemoglobin was lower in patient receiving aprotinin at six
Table 3. Operative Data.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Group previous Aprotinin</th>
<th>Group re-sternotomy Tranexamic acid</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No elective surgery (%)</td>
<td>2.35</td>
<td>6.61</td>
<td>0.211</td>
</tr>
<tr>
<td>CPB time (min)</td>
<td>86.80 ± 31.36</td>
<td>126.29 ± 49.49</td>
<td>0.000</td>
</tr>
<tr>
<td>Cross clamp time (min)</td>
<td>57.74 ± 23.54</td>
<td>84.34 ± 40.47</td>
<td>0.000</td>
</tr>
<tr>
<td>Operative time (min)</td>
<td>201.42 ± 52.55</td>
<td>241.33 ± 69.25</td>
<td>0.000</td>
</tr>
<tr>
<td>Dissection time (min)</td>
<td>66.25 ± 31.83</td>
<td>76.70 ± 31.16</td>
<td>0.028</td>
</tr>
<tr>
<td>MV</td>
<td>12.50 (8 - 18)</td>
<td>8.00 (5 - 18)</td>
<td>0.008</td>
</tr>
<tr>
<td>MV ≥ 48 hours (%)</td>
<td>4.81</td>
<td>14.28</td>
<td>0.028</td>
</tr>
<tr>
<td>ICU</td>
<td>24 (22 - 45)</td>
<td>48 (24 - 72)</td>
<td>0.000</td>
</tr>
<tr>
<td>Postoperative stay</td>
<td>13.86 ± 13.82</td>
<td>13.93 ± 6.90</td>
<td>0.970</td>
</tr>
<tr>
<td>Lactate level</td>
<td>2.77 ± 1.07</td>
<td>2.46 ± 1.26</td>
<td>0.63</td>
</tr>
<tr>
<td>Blood lost H6</td>
<td>187.7 ± 177.7</td>
<td>156.8 ± 112.4</td>
<td>0.13</td>
</tr>
<tr>
<td>Blood lost H20</td>
<td>440 ± 372</td>
<td>432.6 ± 297</td>
<td>0.92</td>
</tr>
<tr>
<td>RBC transfusion (%)</td>
<td>45.88</td>
<td>37.40</td>
<td>0.215</td>
</tr>
<tr>
<td>Reexploration for bleeding</td>
<td>3.53</td>
<td>5.88</td>
<td>0.537</td>
</tr>
<tr>
<td>Postoperative renal failure (%)</td>
<td>5.88</td>
<td>13.33</td>
<td>0.79</td>
</tr>
<tr>
<td>Postoperative stroke (%)</td>
<td>1.17</td>
<td>1.55</td>
<td>1</td>
</tr>
<tr>
<td>Infection (%)</td>
<td>8.23</td>
<td>14.81</td>
<td>0.148</td>
</tr>
<tr>
<td>LOS (%)</td>
<td>9.41</td>
<td>18.38</td>
<td>0.069</td>
</tr>
<tr>
<td>MOF (%)</td>
<td>7.05</td>
<td>11.53</td>
<td>0.279</td>
</tr>
<tr>
<td>30 day mortality (%)</td>
<td>8.23</td>
<td>14.70</td>
<td>0.153</td>
</tr>
<tr>
<td>Inotropic support (%)</td>
<td>10.58</td>
<td>29.41</td>
<td>0.001</td>
</tr>
</tbody>
</table>


hours: 10.39 ± 1.48 vs. 11.08 ± 1.79 (p = 0.004). But the values were similar in both groups at 24 hours: 10.48 ± 1.56 vs. 10.72 ± 1.36 (p = 0.270).

Postoperative platelet counts and fibrinogen level were lower in patient receiving aprotinin than those receiving tranexamic acid with statistically significance at six and 24 hours (p = 0.009, p = 0.000) respectively.

Lower levels of fibrinogen were also found in aprotinin group at six and 24 hours: p = 0.0001, p = 0.0001 respectively.

Mortality is increased in patients treated with TXA 14.7% vs. 8.23% in patients receiving aprotinin: p = 0.153.

4. Discussion

Significant bleeding, especially during redo valve surgery that needs re-exploration and/or requires blood transfusion, increases morbidity and mortality [6].

Hyperfibrinolysis is one of the important contributors to excessive bleeding [9]. There is enough evidence in the cardiac surgical literature to support the beneficial effects of antifibrinolytic agents.
In the present study, we compared the efficacy of low dose aprotinin and tranexamic acid on postoperative blood loss after redo valve surgery and need for red blood transfusion.

Tranexamic acid (30 mg/kg) associated with low dose aprotinin (500,000 kiu) on control bleeding diathesis and transfusion requirement has been studied in other studies.

In our study, both agents reduce blood loss after redo valve surgery. This finding correlates with recent meta-analysis demonstrating equivalent effects of both drugs [10] [11] [12].

Mengistu et al. [13] showed better platelet function measured by whole blood aggregation in the aprotinin group compared to tranexamic acid. In our study, patients in the aprotinin group experienced lower platelet counts than those receiving tranexamic acid either at six and 24 hours after CPB: p = 0.067 p = 0.009 respectively. This finding suggested that tranexamic acid is better in prevention of platelet dysfunction than aprotinin.

In clinical practice, all agents are effective, however controversy regarding which one should be have the potential clinical superiority. Also they are not without side effects.

Use of antifibrinolytic agents must be governed by an appreciation of their inherent risks and benefits. No drug is completely safe, while patient variability also plays an important role in adverse events.

Some studies have suggested that the risk of death and renal failure is increased with the use of aprotinin than with the use of lysine analogues [14] [15] [16] [17]. These adverse events were dramatically observed in Bart study [18] and Bayer withdrawn aprotinin from the world market on May 2008.

The development of postoperative morbidities did not vary significantly between patients receiving low dose aprotinin and those receiving tranexamic acid which is consistent with finding from Van Der Linden’s investigation [19]. Although aprotinin group experienced low morbidity and low mortality compared to tranexamic group, it did not reach statistical significance. However, when examining outcomes of patients treated with tranexamic acid, we found significant longer CPB time, longer ischemic time, prolonged mechanical support, increased proportion of LOS, all these factors might play a part in worse outcome.

In recent study, Montes [20] suggests that in the setting of renal disfunction and low output syndrome, an association between tranexamic acid use and occurrence of postoperative seizures has been demonstrated. In our study, LOS was more prevalent in tranexamic acid group but none had developed convulsive seizures.

It is known that lysine analogues are substantially cheaper than aprotinin [21]. So there are financial reasons to choose the synthetic lysine analogues, and it is routinely used alone in our patients.

Hence, the increased in hospital mortality in the tranexamic group was probably due to LOS and complications in postoperative period, which were more frequent in the aprotinin group.
The retrospective nature of this single institution study constituted the main limitation of this paper. This observational study did not include patients who underwent coronary artery bypass grafting, which may have introduced an additional variance when comparing results between groups. Given the small sample size of our study population, without sufficient statistical power, that makes analysis between groups difficult.

When examining the reason of redo valve surgery, we found that 40.5% of patient receiving low dose aprotinin had previously closed mitral commissurotomy (CMC) and only 26.7% in those receiving tranexamic acid. It is known the previous CMC gives less pleura-pericardic adherences than previous full sternotomy. Also, we know that large dissection of adherences in order to mobilize entire heart, increases the risk of bleeding and makes surgical procedure difficult. This parameter might be taken into account when comparing blood loss between groups.

5. Conclusion

Our results showed that tranexamic acid and aprotinin reduce transfusion need and blood loss. Due to financial reason, we chose tranexamic acid in preventing blood loss in redo valve surgery.

References


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