Randomised placebo controlled double blind study of two low dose aprotinin regimens in cardiac surgery

C R Bailey, A K Wielogorski

Abstract

Objective—To determine whether two low dose aprotinin regimens produce clinically significant reductions in postoperative blood loss compared with a control group.

Design—A randomised double blind placebo controlled study.

Setting—A regional cardiothoracic unit in London.

Patients—79 patients were consecutively allocated to one of three groups. All patients had primary elective surgery with standard anaesthetic and surgical techniques, and no patients were withdrawn from the study.

Interventions—Group K patients (n = 27) received aprotinin (10^6 kallikrein inactivator units (KIU)) into the pump prime whereas group L patients (n = 27) received an intravenous bolus of aprotinin (0.5 × 10^6 KIU) after induction of anaesthesia and 10^6 KIU was added to the pump prime. A third group (group J, n = 25) received 0.9% saline placebo.

Main outcome measures—After insertion of the chest drains at the end of cardiopulmonary bypass, blood losses were measured hourly until the drains were removed 18 to 24 h later. Total haemoglobin loss into the chest drains was calculated.

Results—Both aprotinin treated groups showed significantly less postoperative blood loss than controls (medians: group K, 400 ml; group L, 400 ml; v controls 780 ml; p < 0.001) and there was even less measured postoperative haemoglobin loss within the chest drains in both the aprotinin treated groups than in the controls (medians: group K, 16 g; group L, 19 g; v controls, 47 g; p < 0.001).

Conclusion—In primary cardiac surgery the dose of aprotinin may be reduced by about 80% from the recommended high dose schedule and still significantly reduce postoperative blood loss compared with placebo.

Patients and methods

Ethics committee approval and informed patient consent were obtained. A prospective, placebo controlled, double blind, randomised clinical trial was set up in patients scheduled to have elective cardiac surgery with cardiopulmonary bypass. Patients having repeat operations or with a known previous exposure to aprotinin were excluded from the trial.

DOSE OF APROTININ

Aprotinin is presented in clear vials, each containing 0.5 × 10^6 KIU in 50 ml 0.9% saline solution. One of the investigators (AKW) made up all the test solutions; 500 ml bags of sterile 0.9% saline solutions had a volume discarded and replaced with the same volume of test solution so that all bags contained equal volumes (500 ml). Two freshly drawn up bags were taped together, one labelled "patient bolus", and the other "pump prime" with either the letter J, K, or L. The other investigator (CRB) performed all the patients’ measurements, unaware which group the letters referred to.

With a computer generated random number table, 79 patients were consecutively allocated to one of the following three groups:

Group J: 0.9% saline placebo (n = 25).

These patients received a 500 ml 0.9% bolus of saline solution at intravenous induction of anaesthesia, and a further 500 ml 0.9% saline solution was added to the pump prime.

Group K: 10^6 KIU aprotinin into the pump prime (n = 27). These patients received a bolus of 500 ml 0.9% saline solution at intravenous induction of anaesthesia, and 400 ml 0.9% saline solution plus 100 ml aprotinin

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(10^8 KIU) were added to the pump prime.

Group L: 0.5 × 10^8 KIU aprotinin intravenous bolus to the patient plus 10^8 KIU into the pump prime (n = 27). These patients received 450 ml 0.9% saline solution plus 50 ml aprotinin (0.5 × 10^8 KIU) as a bolus at intravenous induction of anaesthesia, and 400 ml 0.9% saline solution plus 100 ml aprotinin (10^8 KIU) were added to the pump prime.

All patients were premedicated with intramuscular papaveretum (10–20 mg), hyoscine (0–2–0.4 mg), and oral lorazepam (1–2 mg). After intravenous induction of anaesthesia with diazepam and etomidate, intermittent positive pressure ventilation was supplemented with fenoperidine (a narcotic analgesic), pancuronium bromide (a muscle relaxant), and isoflurane (an inhalational anaesthetic agent) as necessary. Porcine mucous heparin (300 IU/kg) was injected into a central vein before cannulation of the heart. Tests for activated clotting time were performed at regular intervals and further heparin given if times fell below 450 seconds.

A hollow fibre membrane oxygenator (Compactflo, Dideco) was primed with 500 ml Gelofusine, 400 ml 5% dextrose, 500 ml compound sodium lactate, 100 ml 50% dextrose, 100 ml 8:4% sodium bicarbonate, 60 ml 20% mannitol, 10 IU neutral insulin, 20 mmol KCl, 5000 IU mucous sodium heparin, and 500 ml trial drugs or placebo. Flows of 2–4 l/min were obtained with a minimally occlusive roller pump and systemic hypothermia to 28–30°C was maintained while the aorta was occluded.

Myocardial preservation during aortic cross clamping was sustained with St. Thomas’ Hospital cardiopulmonary bypass apparatus. Blood samples for activated clotting time, haemoximeter (OSM 2, Radiometer). No cell saver devices were used during the study.

### Table 1 Preoperative demographic data of study groups; mean (SD)

<table>
<thead>
<tr>
<th></th>
<th>Group J (n = 25)</th>
<th>Group K (n = 27)</th>
<th>Group L (n = 27)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>63(10)</td>
<td>62(12)</td>
<td>60(9)</td>
</tr>
<tr>
<td>Sex (M/F)</td>
<td>17/8</td>
<td>16/11</td>
<td>21/6</td>
</tr>
<tr>
<td>Body surface area (m²)</td>
<td>1.78(0.20)</td>
<td>1.82(0.18)</td>
<td>1.87(0.18)</td>
</tr>
<tr>
<td>Haemoglobin (g/dl)</td>
<td>13.9(1.2)</td>
<td>13.4(1.5)</td>
<td>14.2(1.4)</td>
</tr>
<tr>
<td>Platelets (× 10^9)</td>
<td>233(64)</td>
<td>243(85)</td>
<td>223(50)</td>
</tr>
<tr>
<td>APTT ratio;</td>
<td>1.01(0.01)</td>
<td>1.25(0.92)</td>
<td>1.06(0.19)</td>
</tr>
<tr>
<td>PT ratio;</td>
<td>1.02(0.07)</td>
<td>1.01(0.99)</td>
<td>1.00(0.10)</td>
</tr>
<tr>
<td>Patients receiving aspirin within 10 days of operation (n%)</td>
<td>15(60)</td>
<td>12(44)</td>
<td>12(44)</td>
</tr>
<tr>
<td>No of days aspirin was stopped before operation (median interquartile range)</td>
<td>3(2–4)</td>
<td>2(1–7)</td>
<td>3(1–7)</td>
</tr>
<tr>
<td>Patients receiving operation (graft/valve/combination, n)</td>
<td>18/3/4</td>
<td>19/8/0</td>
<td>22/4/1</td>
</tr>
<tr>
<td>Patients receiving internal mammary artery grafts (n %)</td>
<td>14(56)</td>
<td>14(53)</td>
<td>20(74)</td>
</tr>
<tr>
<td>No of distal grafts</td>
<td>2(250)</td>
<td>3(261-411)</td>
<td>2(921)</td>
</tr>
</tbody>
</table>

All differences were non-significant. APTT, activated partial thromboplastin time; PT, prothrombin time.

Results

Table 1 shows the demographic data of the patients studied. There were no significant differences between the groups for age, body surface area, preoperative haemoglobin values, number of distal grafts, or percentage of patients receiving internal mammary artery grafts. Forty four per cent or more of the patients in each group had received regular aspirin within 10 days of their operation, usually up to two or three days before the operation date.

Operative times, intraoperative urine outputs, intraoperative blood loss, and prothrombin sulphate neutralisation dosages were similar in all groups (Table 2).

Table 3 shows the data for postoperative drainage and replacement. There was a significant reduction in the median (interquartile range) of postoperative chest drainage in both the pre-treated groups compared with controls (group K, 400 (250–650) ml; group L, 400 (210–550) ml; v group J, 780 (575–1045) ml; and p < 0.001), and there was an even greater reduction in measured haemoglobin loss.
within the chest drains in both the aprotinin treated groups (group K, 16(10)-24 g; group L, 19(6)-28 g), v group J, 47 (25-99 g; p < 0.001). Patients in group L received significantly less banked blood than both the control group and patients in group K. Percentage changes in haemoglobin concentrations and platelet counts on the first postoperative day and at discharge were similar in all three groups. Sixty per cent of patients in the control group received fresh frozen plasma compared with 19% in both the pretreated groups (p < 0.01), and there was a significantly increased mean prothrombin time ratio in control group patients on the first postoperative day (25% in group J v 12% in group K and 15% in group L, p < 0.02).

Discussion

There is now irrefutable evidence that aprotinin reduces blood loss after cardiac surgery.12 Cardiopulmonary bypass has extensive effects on the mechanism of coagulation that predispose patients to excessive bleeding after surgery, and although the physicochemical effects of aprotinin have been extensively investigated, its mode of action has not yet been fully elucidated. It may act in one or more of the following ways. Firstly, preservation of platelet glycoprotein Ib (GPIb); von Willebrand Factor (vWF) combines with the GPIb receptor to promote platelet adhesiveness, and both plasmin and kallikrein are known to inhibit this reaction. Van Oeveren et al showed that GPIb concentrations are maintained in aprotinin treated patients,3 and so aprotinin may preserve platelet adhesiveness through its antiplasmin and antikallikrein effects. Secondly, attenuation of the intrinsic clotting pathway; kallikrein promotes clotting through the intrinsic pathway, and serum concentrations of aprotinin > 200 KIU/ml inhibit kallikrein and would thus be expected to reduce coagulation. Evidence for this is, however, conflicting. Dietrich et al5 de Smet et al,6 and Lu et al7 all confirmed a reduction in coagulation by showing either preservation of antithrombin III concentrations or a reduction in the plasma antithrombin III activity when aprotinin was used. By contrast, Havel et al found no significant difference in plasma concentrations of thrombin-antithrombin III complexes between patients treated with aprotinin and controls.8 Thirdly, aprotinin may have an antifibrinolytic effect. By inhibiting plasmin-mediated digestion of fibrin, aprotinin reduces fibrinolysis as indicated by lower concentrations of fibrin degradation products and maintained α2 antiplasmin activity. This has been confirmed by Havel et al8 and Blauhut et al9.

All these actions of aprotinin may combine to produce a more satisfactory coagulation profile in patients after bypass.

Most of the previous studies have involved the use of high dose aprotinin, the basis for this coming from studies performed by biochemists working in Germany; they aimed to reach a serum concentration of > 200 KIU/ml of aprotinin. However, aprotinin reduces fibrinolysis as indicated by lower concentrations of fibrin degradation products and maintained α2 antiplasmin activity as early as the second postoperative day.

In our cardiothoracic unit it is the surgeons' policy to continue to prescribe aspirin until admission to hospital, and consequently 50% of patients requiring primary cardiac surgery receive regular aspirin until two or three days before surgery. As Rosyton et al showed significant reductions in postoperative losses in patients pretreated with aspirin who received high dose aprotinin, we thought it was valid to study aprotinin in the population of patients we see who require primary cardiac surgery.10

In view of the concerns about high doses of aprotinin, which may be dose-dependent, we decided to investigate low dose aprotinin regimens.

Our results compare favourably with previously published studies of high dose aprotinin in primary cardiac surgery, with a
50% reduction in volumetric postoperative drainage and an even greater reduction in haemoglobin loss; for example, Friedrich et al showed a reduction in mean postoperative blood loss from 984 ml (control group) to 488 ml (high dose aprotinin group). The results of our study were statistically indistinguishable for both treatment groups and indicate that the use of high dose aprotinin is unnecessary to reach significant reduction in postoperative blood loss after cardiopulmonary bypass in patients who need primary cardiac surgery.

With regard to the use of blood and blood products during the period of the study, it was the transfusion policy in our unit to give blood to achieve a packed cell volume of 35% irrespective of measured losses after operation. Consequently, all patients studied were overtransfused and we now believe, in collaboration with our haematology colleagues, that most patients given low dose aprotinin do not need autologous blood transfusions. Platelet packs, a more appropriate product to give to patients with non-surgical postoperative bleeding, were difficult to obtain in our unit and we acknowledge that some patients were probably given inappropriate fresh frozen plasma. The end point of our study was not to assess differences in the uses of blood and blood products between the groups, however, but simply to record and compare differences in postoperative losses.

From all the aprotinin studies undertaken so far we may speculate on certain features: (a) a patient bolus is required to reduce intraoperative losses, as, if the dose is left until the initiation of bypass, excessive bleeding may occur during dissection, especially in repeat operations. In our study, neither group of pre-treated patients showed a reduction in intraoperative losses when compared with the control group, or the bolus was inadequate (group L). Similarly, Benmosbah et al. gave a dose of 1-75 × 10^6 KIU at aortic cannulation and found no reduction in intraoperative losses, although postoperative losses were reduced compared with a control group. (b) A pump prime bolus seems to be needed to reduce activation of the clotting cascade through contact with the bypass circuit, and to maintain adequate serum concentrations by allowing for the dilutional effects of cardiopulmonary bypass. Royston showed that postoperative losses were related to serum concentrations at the end of bypass, and we postulate that the critical, as yet unknown, serum concentrations may be as low as 50 KIU/ml (the antiplasmin concentration).

Although serum concentrations of aprotinin were not measured, we speculate that if 10^6 KIU aprotinin is added to the pump prime, then assuming a circulating volume of 7 l on bypass, a bypass time of 75 minutes (the mean bypass time in this study was 73 minutes), aprotinin half life of 44 minutes, and zero order kinetics, then the serum concentration of aprotinin will decrease to about 50 KIU/ml by the end of bypass; a concentration sufficient for an antiplasmin, but not an antikallikrein, effect.

Carrel et al gave a patient bolus of 2 × 10^6 KIU at the start of the operation, whereas Locatelli et al gave an infusion of 0.5 × 10^6 KIU/hour with no bolus: both these groups showed no reduction in blood loss, possibly because serum concentrations of aprotinin may not reach the threshold necessary for the end of the bypass period. By contrast, when Carrel et al gave a single bolus of 2 × 10^6 KIU into the pump prime they found reductions in blood loss and transfusion requirements that were identical to reductions obtained with high dose aprotinin.

Kallis et al have shown that aprotinin may be efficacious when given after operation to patients (not pretreated with aprotinin) who bleed excessively after surgery, and in the light of this, we gathered in the study group. We therefore believe that a rational approach would be to give low dose aprotinin to all patients having primary cardiac surgery who have received regular aspirin within 10 days of their operation, and to reserve high dose aprotinin for high risk patients such as those needing repeat procedures. We believe that patients not taking aspirin and having primary myocardial revascularisation do not need intraproductive aprotinin. After operation, however, if significant non-operative bleeding occurs, then these patients may benefit from postoperative aprotinin.

In conclusion, this study shows that in primary cardiac surgery the dose of aprotinin may be reduced by about 80% from the recommended dose schedule and still significantly reduce postoperative blood loss.

We thank Mr J B O’Riordan and Mr F P Shabbott, consultant surgeons, for their co-operation, and the cardiothoracic staff in the operating theatres and intensive care unit for their co-operation, and the cardiothoracic unit for financial assistance towards this research project.

9 Blauhut B, Gross C, Necek S, Doran JE, Spath P, Lundsgaard-Hansen P. Effect of high dose aprotinin on...


