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Randomized placebo-controlled double-blind study of three aprotinin regimens in primary cardiac surgery

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The serine proteinase inhibitor aprotinin significantly reduces postoperative blood loss in patients requiring cardiac surgery using cardiopulmonary bypass. This study compared two low-dose regimens with administration of high-dose aprotinin and a control protocol to determine whether the dose of aprotinin could be greatly decreased but still maintain efficacy after primary cardiac surgery. Some 100 patients were randomly assigned to one of four groups: control group (0·9 per cent saline placebo, $n = 25$); high-dose group (aprotinin 2×10^6 kallikrein inactivator (KI) units intravenous patient bolus and $0{\cdot}5 \times 10^6$ KI units h^{-1} plus 2×10^6 KI units into pump prime, $n = 25$); prime group (aprotinin 2×10^6 KI units added to the pump prime, $n = 24$); and patient group (aprotinin 10^6 KI units intravenous patient bolus plus 10^6 KI units added to the pump prime, $n = 26$). Only patients from the high-dose and patient groups had reduced intraoperative blood loss, but patients from all three aprotinin-treated groups demonstrated a significant decrease in median postoperative blood loss compared with the control group (high-dose 350 ml, prime 420 ml, patient 340 ml *versus* control 780 ml; $P < 0{\cdot}001$). There was an even greater reduction in measured median postoperative haemoglobin loss within the chest drains in the treated compared with the control patients (high-dose 15 g, prime 24 g, patient 14 g *versus* control 47 g; $P < 0{\cdot}001$). These decreases were statistically the same for all the treated groups; it is possible to lower the dose of aprotinin to approximately one-third of the currently recommended dosage and still obtain significantly reduced postoperative blood loss in primary cardiac surgery.

Aprotinin (Trasylol; Bayer, Newbury, UK), a serine proteinase inhibitor, reduces postoperative blood loss after cardiac surgery employing cardiopulmonary bypass[1,2]. Most previous studies have used aprotinin at high dosage (approximately 6×10^6 kallikrein inactivator (KI) units) with the aim of achieving serum levels adequate for a full antikallikrein effect.

The purpose of the present study was to determine whether the dose of aprotinin could be greatly decreased while still producing a clinically significant reduction in postoperative blood loss in patients having primary cardiac surgery. A dose–response study was not used to achieve this; instead the effects of two low-dose aprotinin regimens were compared with those of high-dose aprotinin and those in a control group. By using a lower aprotinin dose than that currently recommended it was intended to reduce the cost per patient, maintain efficacy and possibly extend the use of aprotinin to all patients needing cardiac surgery, not just high-risk patients such as those requiring revisional operations or complex procedures.

Patients and methods

Ethics committee approval and informed patient consent were obtained. A prospective placebo-controlled double-blind randomized trial was set up involving patients scheduled to undergo elective cardiac surgery employing cardiopulmonary bypass. Patients undergoing revisional operations or with a known previous exposure to aprotinin were excluded from the trial.

Aprotinin dosage

Aprotinin is presented in clear vials, each containing $0{\cdot}5 \times 10^6$ KI units in 50 ml 0·9 per cent saline solution. Using a computer-generated random number table, 100 patients were consecutively allocated to one of four groups. One investigator (A.K.W.) made up all the test solutions; a known volume of sterile 0·9 per cent saline was discarded from 500 ml bags and replaced with the same volume of test solution so that all bags contained the same equal volume (500 ml). Six freshly prepared bags were taped together, one labelled 'patient bolus', one labelled 'pump prime' and the other four labelled 'patient infusion'. Each set of bags was given a consecutive number. A separate investigator (C.R.B.) performed all the patient measurements, unaware of to which group the number referred. The four groups are shown in *Table 1* and described below.

Control group (n = 25). Patients received an intravenous bolus of 500 ml 0·9 per cent saline at induction of anaesthesia, followed by 500 ml 0·9 per cent saline every hour; a further 500 ml 0·9 per cent saline was added to the pump prime.

High-dose group (n = 25). Patients received an intravenous bolus of 300 ml 0·9 per cent saline with 200 ml aprotinin (2×10^6 KI units) at induction of anaesthesia, followed by 450 ml 0·9 per cent saline with 50 ml aprotinin ($0{\cdot}5 \times 10^6$ KI units) every hour; a further 300 ml 0·9 per cent saline with 200 ml aprotinin (2×10^6 KI units) was added to the pump prime.

Prime group (n = 24). Patients received an intravenous bolus of 500 ml 0·9 per cent saline at induction of anaesthesia, followed by

Table 1 Aprotinin dosage regimens

Group	Bolus	Infusion	Pump prime
Control	Saline	Saline	Saline
High dose	2×10^6 KI units aprotinin	$0{\cdot}5 \times 10^6$ KI units h^{-1} aprotinin	2×10^6 KI units aprotinin
Prime	Saline	Saline	2×10^6 KI units aprotinin
Patient	10^6 KI units aprotinin	Saline	10^6 KI units aprotinin

KI, kallikrein inactivator

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500 ml 0·9 per cent saline every hour; a further 300 ml 0·9 per cent saline with 200 ml aprotinin (2×10^6 KI units) was added to the pump prime.

Patient group (n = 26). Patients received an intravenous bolus of 400 ml 0·9 per cent saline with 100 ml aprotinin (10^6 KI units) at induction of anaesthesia, followed by 500 ml 0·9 per cent saline every hour; a further 400 ml 0·9 per cent saline with 100 ml aprotinin (10^6 KI units) was added to the pump prime.

Other procedures

All patients received premedication with intramuscular papaveretum 10–20 mg and hyoscine 0·2–0·4 mg, and oral lorazepam 1–2 mg. After induction of anaesthesia with intravenous diazepam and etomidate, intermittent positive-pressure ventilation was supplemented with phenoperidine (a narcotic analgesic), pancuronium (a muscle relaxant) and isoflurane (an inhalational anaesthetic agent) as necessary. Porcine mucous heparin (300 units kg^{-1}) was injected into a central vein before cannulation of the heart.

Tests of activated clotting time were performed at regular intervals and further heparin was given if this fell below 450 s.

A hollow-fibre membrane oxygenator (Compactflo; Dideco, Mirandola, Italy) was primed[3] with 500 ml Gelofusine (Consolidated Chemicals, Wrexham, UK), 500 ml 5 per cent dextrose, 500 ml compound sodium lactate, 100 ml 50 per cent dextrose, 100 ml 8·4 per cent sodium bicarbonate, 60 ml 20 per cent mannitol, 10 units Actrapid (Novo Nordisk, Crawley, UK), 20 mmol potassium chloride, 5000 units mucous sodium heparin and 500 ml trial drugs or placebo. Flows of 2·4 l m^{-2} min^{-1} 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 cardioplegic solution injected into the aortic root at 0°C. Mean arterial pressure during bypass was kept between 50 and 80 mmHg with nitroglycerin, supplemented with phentolamine or metaraminol as necessary. After rewarming to 37°C at the completion of operation and discontinuation of bypass, the residual effects of heparin were neutralized with protamine sulphate.

After transfer to the intensive care unit, intermittent positive-pressure ventilation was continued until the patient was warm peripherally, was not bleeding and was otherwise stable. To maintain adequate filling pressures, blood was given if the measured haematocrit was less than 35 per cent and Gelofusine if it was greater than 35 per cent. Fresh frozen plasma was given if the measured clotting ratio was greater than 1·5 times the control value, platelet packs were infused if the platelet count was less than 100×10^9 l^{-1}, and 1 ml kg^{-1} h^{-1} crystalloid fluid was given.

Measurements

Blood samples were taken before operation, after induction of anaesthesia, every 30 min during bypass, before and after protamine administration, before transfer to the intensive care unit and at regular intervals while the patient was in intensive care, and at 24 h and 7 days after operation.

Haemoglobin concentration, platelet count and clotting were measured by routine laboratory methods. Blood loss during the operation into the swabs and suction apparatus was recorded both before and after bypass (recorded as intraoperative losses), while mediastinal blood shed during bypass was reinfused together with all the remaining volume in the cardiopulmonary bypass reservoir at the end of bypass. After insertion of chest drains, losses were measured hourly until drain removal 18–24 h later (recorded as postoperative losses). Because individual drainage volumes can vary in haemoglobin content, total haemoglobin loss into the chest drains was calculated using a haemoximeter (OSM 2; Radiometer, Crawley, UK). No cell saver devices were used during the study.

Table 2 Demographic data

	Control (*n* = 25)	High dose (*n* = 25)	Prime (*n* = 24)	Patient (*n* = 26)
Age (years)*	63(10)	64(13)	59(11)	63(10)
Sex ratio (M:F)	17:8	18:7	17:7	20:6
Body surface area (m^2)*	1·78(0·20)	1·80(0·20)	1·87(0·18)	1·82(0·17)
Preoperative haemoglobin level (g dl^{-1})*	13·9(1·2)	14·5(1·5)	14·0(1·7)	14·1(1·7)
Preoperative platelet count ($\times 10^9$ l^{-1})*	213(64)	222(60)	227(74)	216(43)
Preoperative APTT ratio*	1·01(0·11)	1·28(0·82)	1·11(0·20)	1·04(0·13)
Preoperative PT ratio*	1·02(0·07)	1·02(0·07)	1·03(0·06)	1·03(0·07)
Patients receiving aspirin within 10 days of operation	15	13	13	14
Median (i.q.r.) no. of days aspirin was stopped before operation	3 (2–4)	2 (1–3)	3 (2–3)	2 (2–3)
Operation type (graft:valve:combination) (no. of patients)	18:3:4	17:5:3	17:4:3	19:5:2
No. of patients receiving internal mammary artery grafts	14	10	13	12
No. of distal grafts*	3·59(2·50)	3·70(2·15)	3·50(2·96)	3·37(2·25)

*Values are mean(s.d.). APTT, activated partial thromboplastin time; PT, prothrombin time; i.q.r., interquartile range

Table 3 Operation data

	Control (*n* = 25)	High dose (*n* = 25)	Prime (*n* = 24)	Patient (*n* = 26)	*P*
Time from induction of anaesthesia to cardiopulmonary bypass (min)*	83(24)	86(23)	93(28)	83(25)	> 0·05
Cardiopulmonary bypass time (min)*	72(21)	74(33)	70(22)	67(16)	> 0·05
Ischaemia time (min)*	38(14)	44(23)	41(16)	39(14)	> 0·05
Time from end of bypass to ICU transfer (min)*	70(25)	72(22)	65(28)	68(15)	> 0·05
Median (i.q.r.) intraoperative urine output (ml)	830 (500–1150)	940 (690–1325)	730 (515–1150)	770 (530–1020)	> 0·05
Median (i.q.r.) intraoperative blood loss (ml)	950 (700–1280)	690 (400–1000)	900 (630–1215)	580 (490–790)	< 0·01†
Protamine:heparin ratio (mg:100 units)*	1·36(0·36)	1·50(0·43)	1·49(0·44)	1·48(0·36)	> 0·05

*Values are mean(s.d.). ICU, intensive care unit; i.q.r., interquartile range. †High-dose group *versus* control and prime groups; patient group *versus* control and prime groups (Mann–Whitney *U* test)

Table 4 Postoperative data

	Control ($n=25$)	High dose ($n=25$)	Prime ($n=24$)	Patient ($n=26$)	P
Median (i.q.r.) postoperative chest drainage (ml)	780 (575–1045)	350 (215–570)	420 (290–550)	340 (200–460)	<0·001*
Median (i.q.r.) haemoglobin loss in drains (g)	47 (25–99)	15 (10–27)	24 (15–32)	14 (9–21)	<0·001*
Patients requiring blood replacement					<0·002†
0 units	0	2	2	3	
1 unit	0	2	2	1	
2 units	5	8	7	10	
⩾3 units	20	13	13	12	
Median (i.q.r.) no. of blood units transfused per patient	3 (3–5)	3 (2–4)	3 (2–4)	2 (2–3)	
Mean(s.d.) haemoglobin concentration on day 7 after operation (g dl^{-1})	11·9(1·3)	12·9(1·3)	12·2(1·7)	12·5(1·9)	>0·05
Mean(s.d.) platelet count on day 7 after operation ($\times 10^9$ l^{-1})	280(87)	249(79)	224(88)	238(95)	>0·05
Patients given fresh frozen plasma					<0·01†
0 units	10	22	18	22	
2 units	13	2	6	3	
4 units	1	1	0	0	
6 units	1	0	0	1	
Median (i.q.r.) no. of fresh frozen plasma units transfused per patient	2 (2–2)	0 (0–0)	0 (0–2)	0 (0–0)	
Mean(s.d.) increase in APTT ratio on day 1 after operation (%)	15(16)	14(36)	7(11)	12(62)	>0·05
Mean(s.d.) increase in PT ratio on day 1 after operation (%)	25(19)	13(13)	11(24)	10(13)	<0·02‡

APTT, activated partial thromboplastin time; PT, prothrombin time; i.q.r., interquartile range. *Control *versus* all other groups (individual analysis by Mann–Whitney U test); †control *versus* all other groups (Fisher's exact test); ‡control *versus* all other groups (individual analysis by ANOVA)

Statistical analysis

Normally distributed data were assessed by analysis of variance (ANOVA). Intraoperative and postoperative losses were initially analysed using the Kruskal–Wallis test and then subjected to the Mann–Whitney U test to determine intergroup differences. Nominal data were assessed by χ^2 or Fisher's exact test. Significance was assumed at $P<0·05$.

Results

Table 2 shows demographic data. The groups were well matched in terms of age, body surface area, preoperative haematological values, number of distal grafts and percentage of patients receiving internal mammary artery grafts. Some 52 per cent or more of the patients in each group had received regular aspirin within 10 days of operation, usually up to 2 or 3 days before the operation date.

Operating time, intraoperative urine output and protamine neutralization dosage were similar in all groups (*Table 3*). Those in both the high-dose and patient groups had significantly reduced intraoperative blood loss compared with patients in the other two groups. *Table 4* gives data for postoperative drainage and replacement. There was a significant reduction in median (interquartile range (i.q.r.)) postoperative chest drainage volume in all the pretreated groups compared with controls (high-dose, 350 (215–570) ml; prime, 420 (290–550) ml; patient, 340 (200–460) ml; *versus* control, 780 (575–1045) ml ($P<0·001$)). There was an even greater decrease in measured median (i.q.r.) haemoglobin loss within the chest drains in all the aprotinin-treated groups (high-dose, 15 (10–27) g; prime, 24 (15–32) g; patient, 14 (9–21) g; *versus* control, 47 (25–99) g ($P<0·001$)) (*Fig. 1*).

All aprotinin-treated groups received significantly less banked blood than the control group. Percentage changes in haemoglobin level and platelet count on day 1 after operation were similar in all groups, and both mean haemoglobin concentration and platelet count were similar in all four groups at discharge. Some 60 per cent of patients in the control group received fresh frozen plasma, compared with 12 per cent in the high-dose group, 25 per cent in the prime group and 16 per cent in the patient group ($P<0·01$). There was a significantly increased mean prothrombin time ratio in the control group on day 1 after operation (mean increase 25 per cent *versus* 13 per cent in the high-dose group, 11 per cent in the prime group and 10 per cent in the patient group; $P<0·02$).

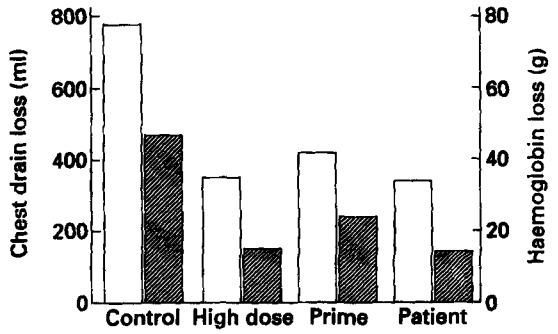

Fig. 1 Measured median postoperative chest drain (□) and haemoglobin (▨) losses

Discussion

There is now irrefutable evidence that aprotinin therapy reduces blood loss after cardiac surgery[1,2]. Cardiopulmonary bypass has extensive effects on the mechanism of coagulation that predispose patients to excessive bleeding after surgery

but, although the physicochemical effects of aprotinin administration have been extensively investigated, its mode of action has not yet been fully elucidated. Aprotinin may act in one or more of the following ways: preservation of platelet glycoprotein 1b to maintain platelet adhesiveness[4], attenuation of the intrinsic clotting pathway[5-7] and antifibrinolysis[8,9].

Most previous studies have involved the use of high-dose aprotinin on the basis of work performed in Germany, which aimed to achieve a serum level greater than 200 KI units ml^{-1} for full antikallikrein activity (antiplasmin activity is achieved at the lower level of 50 KI units ml^{-1}). In the present study the use of aprotinin in patients undergoing primary cardiac surgery was investigated because in this unit more than 50 per cent of such patients receive regular aspirin until 2 or 3 days before operation and Royston *et al.*[10] have demonstrated a significant reduction in postoperative blood loss in patients pretreated with aspirin who received high-dose aprotinin.

It was decided to investigate low-dose aprotinin regimens because, although Bidstrup *et al.*[11] have suggested that aprotinin in high dosage does not increase the incidence of subsequent graft occlusion, this is controversial. Bohrer *et al.*[12] have reported aprotinin-associated thrombus formation, and Samama *et al.*[13] demonstrated an increase in the rate of spontaneous femoral artery thrombosis in pigs treated with aprotinin, compared with a control group. Any such potential problems may be dose dependent.

The present results compare favourably with those of previously published studies using high-dose aprotinin in primary cardiac surgery, showing a 50 per cent reduction in volumetric postoperative drainage and an even greater decrease in haemoglobin loss. For example, Fraedrich *et al.*[14] demonstrated a reduction in mean postoperative blood loss from 984 ml (control group) to 488 ml (high-dose aprotinin group). The results of the present study were statistically the same for all treated groups and indicate that high-dose aprotinin is unnecessary to achieve a statistically significant decrease in postoperative blood loss after cardiopulmonary bypass in patients requiring primary cardiac surgery.

Since this study, Hunt *et al.*[15] have shown that aprotinin affects activated clotting time and have recommended that this time should be maintained at the higher value of 750 s when aprotinin is used. Despite activated clotting time being maintained at the lower value of 450 s during the present study, there was no clinical evidence of graft occlusion in any patient pretreated with aprotinin.

With regard to blood and blood-product usage, during the period of the study it was policy to administer blood to achieve a haematocrit of 35 per cent, irrespective of measured postoperative losses. Consequently all patients were relatively overtransfused and we now believe that most patients given low-dose aprotinin do not require autologous blood transfusion. Platelets, which are a more appropriate product to administer to patients with non-surgical postoperative bleeding, were difficult to obtain and it is acknowledged that some patients were probably inappropriately given fresh frozen plasma. However, the endpoint of the study was not to assess differences in blood and blood-product usage between the groups but to record and compare differences in postoperative losses.

From all the aprotinin studies undertaken so far one might speculate on certain features. A patient bolus is required to reduce intraoperative losses, because if this is left until the initiation of bypass excessive bleeding may occur during dissection, especially in revisional operations. In the present study, patients in both the high-dose and patient groups displayed a reduction in intraoperative losses compared with those in the control group, probably because aprotinin was given early in the course of the operation. Patients in the prime group, who received aprotinin only in the pump prime, did not demonstrate a reduction in intraoperative losses, which confirms work performed by Benmosbah *et al.*[16] who gave approximately $1{\cdot}75 \times 10^6$ KI units at aortic cannulation and found no decrease in intraoperative losses, although postoperative losses were reduced compared with a control group. A pump prime bolus seems to be required to reduce activation of the clotting cascade through contact with the bypass circuit and to maintain adequate serum levels by allowing for the dilutional effects of cardiopulmonary bypass. Royston[17] demonstrated that postoperative losses were related to serum levels at the end of bypass and we postulate that the critical, as yet unknown, serum level may be as low as 50 KI units ml^{-1} (i.e. the antiplasmin level).

Although serum levels of aprotinin were not measured, one might speculate that, if 10^6 KI units aprotinin is added to the pump prime, assuming a circulating volume of 7 litres on bypass, a bypass time of 75 min (the mean time in this study was 73 min), an aprotinin half-life of 44 min and zero-order kinetics, the serum level of aprotinin will decrease to approximately 50 KI units ml^{-1} by the end of bypass. This is a level sufficient for an antiplasmin, but not antikallikrein, effect. Carrel *et al.*[18] gave a patient bolus of 2×10^6 KI units at the start of operation, while Locatelli *et al.*[19] gave an infusion of $0{\cdot}5 \times 10^6$ KI units h^{-1} with no bolus. Both these groups failed to demonstrate a reduction in blood loss, possibly because serum levels of aprotinin were inadequate at the end of the bypass period. In contrast, when Carrel *et al.*[18] gave a single bolus of 2×10^6 KI units into the pump prime there was a decrease in blood loss and transfusion requirements that was identical to the reduction obtained using high-dose aprotinin. Patients in the two low-dose regimens in the present study received either 10^6 or 2×10^6 KI units aprotinin into the pump prime, both doses being high enough to maintain antiplasmin serum levels at the end of bypass.

Kallis *et al.*[20] have shown that aprotinin may be effective when given after operation to patients not pretreated with aprotinin who bleed excessively following surgery. In view of the present results, we believe that a rational approach would be to give low-dose aprotinin to all patients undergoing primary cardiac surgery who have received regular aspirin within 10 days of operation and to reserve high-dose aprotinin for high-risk patients, such as those requiring revisional procedures. Patients not taking aspirin and undergoing primary myocardial revascularization do not require intraoperative aprotinin. After surgery, if significant non-surgical bleeding occurs, these patients may benefit from postoperative aprotinin therapy.

In conclusion, this study has demonstrated that, in primary cardiac surgery, all three aprotinin dosages produced equivalent reductions in postoperative blood loss compared with controls. The dose of aprotinin may, therefore, be reduced to approximately one-third of the conventionally recommended value and still produce a significant decrease in postoperative blood loss in patients requiring primary cardiac surgery.

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