POSTOPERATIVE USE OF APROTININ IN CARDIAC OPERATIONS: AN ALTERNATIVE TO ITS PROPHYLACTIC USE

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Background: Aprotinin reduces blood loss after cardiopulmonary bypass. Although there can be little doubt about the efficacy of aprotinin, its safety has been questioned recently and is still under investigation. Because of the potential for complications and the high cost, a selective strategy limiting drug delivery to patients with established postoperative bleeding will be more reasonable. **Methods:** In a prospective, randomized, double-blind trial we studied the effect of postoperative low-dose (2 million kallikrein inactivator units) aprotinin on blood loss and transfusion requirements in patients undergoing cardiopulmonary bypass. Fifty-seven patients were randomly assigned to two groups: aprotinin or placebo. **Results:** The two groups were comparable in all demographic and surgical variables. Postoperative chest tube drainage was significantly less in the aprotinin group than in the placebo group (410 ml vs 696 ml, $p < 0.01$). The use of homologous blood products was significantly less in the aprotinin group than in the placebo group (0.4 ± 0.5 unit vs 1.7 ± 0.9 unit for packed red blood cells and 0.8 ± 1.3 unit vs 2.3 ± 1.6 unit for fresh frozen plasma). **Conclusions:** Our results suggest that postoperative aprotinin reduces blood loss and transfusion requirements and provides the opportunity to restrict its use selectively to patients with excessive postoperative bleeding. (J Thorac Cardiovasc Surg 1996;112:1462-7)

The serine proteinase inhibitor aprotinin has been demonstrated to decrease postoperative bleeding and transfusion requirements in patients undergoing cardiac operations with cardiopulmonary bypass (CPB).¹ Since the first description of high-dose aprotinin for prophylaxis against excessive postoperative bleeding, numerous studies with different dosage protocols have been published that confirmed the efficacy of the drug.²⁻⁴ It has been suggested that aprotinin should be given before and during CPB to produce a constant plasma concentration to prevent fibrinolysis and to protect platelet function.

Although initial clinical reports suggested aprotinin to be safe with few side effects, evidence has recently appeared that questions its overall safety for prophylactic systemic therapy. Adverse effects on coronary artery bypass graft patency, renal impairment, anaphylactic reactions during subsequent exposures, and disseminated intravascular coagulation after profound hypothermia have been attributed to the systemic use of aprotinin.⁵⁻⁷ The cost of a high-dose aprotinin regimen is equivalent to the cost of about 8 to 10 units of blood.⁸ The high cost of aprotinin restricts routine prophylactic use in many centers, especially in the United States, because of potential limitations in reimbursement to all health care providers.⁹

Excessive bleeding after cardiac operations is a major concern for cardiac surgical teams. It has been reported in 5% to 25% of patients undergoing CPB.¹⁰ This figure becomes more important in view of the increasing number of reoperations and emergency surgical procedures during which patients are still under the effect of antiplatelet or antifibrinolytic agents. However, only 3% to 5% of all patients undergoing cardiac operations require reoperation for bleeding.¹¹ This supports our contention that the

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Table I. Operative procedures performed

Operations	Aprotinin group (n = 29)	Placebo group (n = 28)
CABG	19	17
AVR or MVR	5	8
DVR	4	3
CABG-AVR	1	—

CABG, Coronary artery bypass grafting; AVR, aortic valve replacement; MVR, mitral valve replacement; DVR, double valve replacement (AVR and MVR).

majority of patients who are treated with aprotinin are unnecessarily exposed to side effects of the drug. It would be prudent to apply aprotinin on a more selective basis to avoid adverse reactions and unnecessary prophylactic use. One effective strategy to achieve these goals would be to restrict the use of aprotinin exclusively to patients with established postoperative bleeding. Angelini and colleagues¹² reported six cases in which aprotinin postoperatively reduced bleeding that failed to respond to conventional treatment. More recently, Kallis and associates¹³ demonstrated that postoperative use of aprotinin in patients with established bleeding reduced blood loss. However, further studies are warranted on this topic.

This clinical randomized double-blind study was conducted to investigate the effect of aprotinin given postoperatively on blood loss and transfusion requirements in patients undergoing cardiac operations.

Patients and methods

A randomized, double-blind, placebo-controlled study was carried out to compare the efficacy of postoperative aprotinin and placebo to decrease bleeding and transfusion requirements on patients undergoing cardiac operations with CPB. Informed consent was obtained from all patients. Patients who had previous exposure to aprotinin or who had received systemic or topical aprotinin during the operation were excluded from the study. Fifty-seven patients were included in the study and were randomized to receive aprotinin or placebo by means of the table of random numbers.

Aprotinin group. Patients in the aprotinin group received a bolus of 2×10^6 kallikrein inhibiting units (KIU) of aprotinin (280 mg) (Trasylol; Bayer AG, Leverkusen, Germany) infused over 15 minutes when they arrived in the intensive care unit (ICU).

Placebo group. Patients in the placebo group received an equal volume of normal saline solution at all corresponding times.

The operative procedures performed are defined in Table I. All patients were operated on and cared for by the same team.

Table II. Patient characteristics*

Variable	Aprotinin	Placebo
n	29	28
Age (yr)	51.6 ± 15.4	48.2 ± 14.2
Male/female	21/8	19/9
Preop. aspirin (n)	14	13
CPB time (min)	97.5 ± 45.6	78.4 ± 25.5
No. of grafts	2.8 ± 0.7	2.6 ± 0.7
No. of ITAs	0.9 ± 0.2	0.7 ± 0.4

*Values are mean ± standard deviation. No significant differences were observed in patient characteristics.

The anesthetic management and conduct of CPB were standardized. The extracorporeal circuit consisted of a hollow-fiber membrane oxygenator (Terumo Copiox E, Terumo Co., Tokyo, Japan). Polyvinyl chloride tubing was used throughout the circuit except for the roller pump tubing, which was silicone rubber. Before CPB patients were given 300 U bovine lung heparin per kilogram of body weight; whenever the activated clotting time was shorter than 480 seconds, additional doses of heparin were given.

Mild to moderate hypothermia, cold crystalloid cardioplegic solution (Plegisol, Abbott Laboratories, North Chicago, Ill.) for induction of cardioplegia, and cold blood cardioplegic solution (infused every 20 minutes) for maintenance were used for myocardial protection. Before unclamping the aorta, we administered warm blood cardioplegic solution (500 ml at 37° C). The cardioplegic solution (either crystalloid or blood cardioplegic solution) was returned to the circuit. Left internal thoracic artery grafts were used routinely in patients undergoing coronary artery bypass grafting. The saphenous vein was harvested as needed. During systemic heparinization, blood was routinely returned to the pump-oxygenator and reinfused. Finally, all blood remaining in the venous tubing and in the oxygenator after CPB was collected and reinfused when necessary, during the operation or in the ICU. At the end of CPB, the heparin effect was reversed with protamine sulfate at a 1:1 ratio.

Hemoglobin concentration, hematocrit value, platelet count, prothrombin time, activated partial thromboplastin time, and fibrinogen levels were measured in all patients before the operation and when they arrived at the ICU. The shed mediastinal blood was collected in a commercially available volumetric collection system, and the amount was measured every half hour for the first day and hourly thereafter. The mediastinal and thoracic drains were removed when the total drainage was less than 100 ml over the previous 8 hours.

Homologous packed red cells were administered only when the hematocrit value fell to less than 24%. Patients received fresh frozen plasma when excessive blood loss was accompanied by a prolonged (>1.5 times normal values) prothrombin time. Additional protamine was administered if the activated clotting time/control ratio was greater than 1.5. Platelet transfusions were not used. Shed blood was not autotransfused in any of the patients during this study. Reoperation for bleeding was undertaken if the

Fig. 1. A, Hourly blood loss for the first 6 hours after the initiation of aprotinin or placebo. Values are shown as mean $\pm$ standard error of the mean. B, Cumulative blood loss in the first 6 hours.

blood loss exceeded 500 ml for two consecutive hours without signs of decreasing despite appropriate therapy.

CPB time, total operation time, amount of total chest tube drainage, prevalence of reoperation for bleeding, cause of bleeding, and need for donor blood transfusion or fresh frozen plasma were recorded for all patients. The course of the blood hemoglobin content during hospitalization was analyzed in each patient.

Sample size was calculated by an expected difference in blood loss between groups of 250 ml, standard deviation of 250 ml, $\alpha = 0.05$, $\beta = 0.05$, with $n = 28$ for each of the groups. All results are expressed as the mean values $\pm$ standard deviation. Statistical comparisons were made by means of the Student's t test. A p

value less than 0.05 was considered to be statistically significant. Statistical analyses were made with the use of the Primer of Biostatistics: The Program Version 3.02 (McGraw-Hill, Inc., New York, N.Y.) statistical software package.

Results

No differences were found between the aprotinin and placebo groups in patient age, sex, CPB time, and duration of operation. Fourteen patients in the aprotinin group and 13 in the placebo group had taken aspirin up until 7 days before the operation. Also, the number of bypass grafts and the number of

Table III. Total transfusion requirement

Variable	Aprotinin	Placebo	p Value
Packed RBC (units per patient)	0.45 ± 0.50	1.70 ± 0.9	<0.01
FFP (units per patient)	0.80 ± 1.36	2.35 ± 1.6	<0.01
Patients receiving transfusions (%)	37	64	<0.01

Values are mean ± standard deviation.

internal thoracic arteries used per patient in patients undergoing coronary artery bypass graft operations were not statistically different between the groups (Table II). The types of operative procedures performed were comparable for the two groups. Except for one operation in the aprotinin group, these procedures were initial operations. There were also no significant differences between the groups in postoperative hemodynamics, duration of stay in the ICU, and postoperative hospital stay (data not shown). One patient in the aprotinin group was reoperated on for excessive bleeding. A sternal bleeding site was identified. There were no instances of renal impairment, perioperative myocardial infarction, or allergic reactions to aprotinin.

Fig. 1 shows the course of blood loss after commencement of aprotinin therapy. Postoperative blood loss at 1 hour was 82.5 ± 60.7 ml in the placebo group and was significantly lower in the aprotinin group (40.7 ± 51.5 ml). The trend in the reduction of blood loss continued in the aprotinin group throughout the first 6 hours and thereafter. Significantly less postoperative chest tube drainage was noted in the aprotinin group (including one patient who required reentry for surgical bleeding) than in the placebo group at the first 24-hour measurement (410.5 ± 174.8 ml vs 696.2 ± 247.7 ml, $p < 0.01$) and at the removal of chest tubes (436.8 ± 188.2 ml vs 852.5 ± 336.9 ml, $p < 0.01$). The 95% confidence interval for difference in total blood loss was 271.4 to 559.8 ml.

The use of banked donor blood products during the operation was not significantly different between the groups. Hemoglobin values were similar in the two groups on arrival in the ICU, allowing a direct comparison between groups with regard to postoperative use of blood products. However, the transfusion requirement was significantly lower in the aprotinin group than in the placebo group (Table III). Only 37% of aprotinin-treated patients required donor blood or blood products

Table IV. Hematologic values and coagulation tests

	Aprotinin	Placebo
Hemoglobin (gm/dl)		
Preoperative	13.2 ± 1.1	12.5 ± 1.4
Postoperative	8.9 ± 1.1	8.6 ± 1.2
Platelets ($10^9/L$)		
Preoperative	287.2 ± 84.9	244.8 ± 88.6
Postoperative	136.2 ± 50.9	138.0 ± 60.6
Fibrinogen (mg/dl)		
Preoperative	424.0 ± 92.8	374.1 ± 140.3
Postoperative	312.3 ± 72.8	290.9 ± 84.7
Prothrombin time (sec)		
Preoperative	13.2 ± 0.5	13.3 ± 1.2
Postoperative	13.3 ± 0.8	13.7 ± 1.0
Partial thromboplastin time (sec)		
Preoperative	36.8 ± 4.2	35.3 ± 3.2
Postoperative	38.8 ± 2.9	39.5 ± 2.2

*Values are mean ± standard deviation. No significant differences were observed.

in comparison with 64% of those in the placebo group.

There were no statistically significant differences between the two groups with regard to platelet count, prothrombin time, activated partial thromboplastin time, and fibrinogen level before and early after the operation when patients arrived in the ICU (Table IV).

Discussion

Of all the drugs used to minimize postoperative bleeding, aprotinin has been the most successful. No other blood conservation agent has a comparable efficacy.^{9, 14} However, a consensus has not been reached concerning patient selection and dosage regimen. Numerous reports have shown the benefits of both high-dose and low-dose regimens. Because of the potential for complications and the high cost of aprotinin, it is logical to use aprotinin on a more selective basis, that is, in patients with established postoperative bleeding.

This study demonstrated that postoperative blood loss and transfusion requirements were significantly lower in the aprotinin group than in the placebo group. The satisfactory reduction in postoperative blood loss in the aprotinin group prompted us to analyze the results of blood loss in a smaller subgroup of patients undergoing coronary artery bypass who continued to take aspirin until 1 week before the operation. Aprotinin treatment in these patients significantly decreased the postoperative blood loss. The mean blood loss in the aprotinin group was 460.7 ± 174.7 ml and in the placebo group, $960.7 \pm$

305.2 ml; ($p < 0.01$). In the present study we used the low-dose regimen (2 million KIU) because low-dose aprotinin is sufficient to obtain the required antiplasmin effect and to preserve glycoprotein Ib receptors.^{15, 16} The reduction of postoperative blood loss, to our surprise, is comparable with that in other studies in which aprotinin was applied prophylactically.^{1, 2} The most effective time to administer aprotinin during cardiac operations is still unknown. It has been universally recommended and accepted that aprotinin should be given before CPB and throughout the surgical procedure to be effective.^{17, 18} Gram and colleagues¹⁹ suggested that significant amounts of tissue-type plasminogen activator are incorporated into fibrin generated after neutralization of heparin and thereby may cause the degradation of cross-linked fibrin until at least 24 hours after the operation, although tissue-type plasminogen activator has returned to baseline levels much earlier. Valen and associates²⁰ also reported that increased fibrinolytic activity persists after CPB. The presence of fibrin or fibrin monomers stimulates fibrinolytic activity 100-fold.²¹ This increased activity creates a positive feedback cascade and increases the risk of postoperative bleeding. Aprotinin may influence hyperfibrinolysis in the early postoperative period. However, quantification of plasmin levels is essential to detect the postoperative fibrinolytic state and aprotinin effect.

Kallis and associates¹³ have recently demonstrated the efficacy of aprotinin on hemostasis when used postoperatively on patients who bled significantly. The tissue plasminogen activator antigen decreased and fibrinogen level increased in the aprotinin group. Aprotinin also increased the platelet surface expression of glycoprotein Ib (36% vs 5%, $p < 0.01$) and maintained the platelet von Willebrand factor activity. They suggested that aprotinin, by inhibiting excessive fibrinolysis and reducing plasmin levels, allows replenishment of the platelet surface glycoprotein Ib receptors from intraplatelet pools. Michelson and Barnard²² also have shown that platelets recover from plasmin as soon as it is neutralized by redistribution of the platelet glycoprotein Ib receptor. On the basis of current information, one could expect that postoperative aprotinin would restore platelet function through its antiplasmin effect.

The intact endothelium is involved in the regulation of hemostasis and thrombosis. It is known that endothelial dysfunction occurs systemically during CPB.²³ Aprotinin has been shown to inactivate

protein C, which is the major regulatory protein of thrombus formation.²⁴ Besides controlling the thrombin formation, protein C promotes fibrinolysis by inactivating the plasminogen activator inhibitors.²⁵ The time course of endothelial dysfunction has not been established. Endothelial dysfunction of sublethal and long-lasting character may occur even without morphologic changes²³ and cause leakage of tissue-type plasminogen activator stores after CPB, resulting in a hyperfibrinolytic state. Postoperative aprotinin may also exert an antifibrinolytic action by modulating endothelial cell function. However, the mechanism of this complex interaction requires more comprehensive investigations.

Conclusions

1. Aprotinin is effective even if administered after activation of the hemostatic system, with a consequent significant reduction in blood loss and transfusion requirements.

2. Efficacy of postoperative infusion also provides the opportunity to minimize the overzealous use of prophylactic aprotinin and restrict its use selectively to patients with established postoperative bleeding.

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