
EFFECTS OF APROTININ IN OPEN HEART SURGERY*

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Postoperative blood drainage and blood transfusion has its own complications in open heart surgery. Cardiopulmonary bypass (CPB) is associated with activation of humoral amplification systems, initiating the kallikrein-bradykinin system, resulting fibrinolysis, release of proteases, platelet dysfunction and granulocyte stimulation. These proteases may affect platelets and stimulate granulocytes. The effects of aprotinin on hemostasis were investigated on two study groups, consisting of 30 patients undergoing coronary artery bypass surgery. In group A, a total amount of 1.500.000 kallikrein inactivator units (KIU) was infused before, during, and after weaning from CPB. The second group served as the control group. Chest tube drainage was significantly reduced in group A (530 ± 130 ml, $p < 0.001$). Group A received less bank blood transfusion postoperatively with 13 of the 30 patients receiving none, while 22 patients in group B required more blood transfusion (860 ± 105 ml, $p < 0.001$). Aprotinin could be accepted as a useful adjunct in patients those CPB is applied.

Key words: cardiopulmonary bypass, kallikrein-bradykinin system, fibrinolysis, aprotinin.

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Bleeding remains as a troublesome complication of open heart surgery. It was reported recently that, in one North American hospital, cardiac surgical cases accounted for over a quarter of all of the blood transfused in one year¹. Similarly, 50-60% of patients having cardiothoracic surgery in the United Kingdom requires two to four units of homologous bank blood². During CPB, platelet count decreases, partly because of haemodilution and also as a result of aggregation due to platelet contact with non-biological surfaces, and sequestration in the liver or spleen³. In addition, the remaining platelets may be damaged, and their function impaired, after CPB⁴.

The effects of aprotinin^a was investigated on postoperative blood drainage and transfusion requirement, haematocrit, platelet count, plasma fibrinogen levels in patients undergoing coronary bypass surgery.

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Material and Methods

The effects of Aprotinin in two different groups on patients undergoing primary coronary artery bypass grafting was studied. Each group consisted of 30 patients, in which aprotinin was applied (group A), and control group (Group B). Aprotinin (Trasylol®) was supplied in bottles containing 50 ml solution, each milliliter containing 10.000 kallikrein inactivator units (KIU).

A total amount of 1.5×10^6 KIU was infused to group A. 0.5×10^5 KIU was infused during induction of anesthesia, 0.5×10^5 KIU was added to the priming volume, and 0.5×10^5 KIU was administered after weaning from CPB.

A standard anaesthetic technique was applied in all cases. Heparin (300 iu/kg) was given intravenously before cannulation of the aorta. When the activated clotting time was shorter than 400 seconds, additional heparin (100 iu/kg) was given. Protamine sulfate was administered within 10 minutes after weaning from CPB. Mean perfusion flow rate was 2.4 L/min/m², and moderate systemic hypothermia was applied to 26-28°C.

In all of the patients, non pulsatile centrifugal pumps^b and membrane oxygenators^c were used. Priming was done with crystalloid solutions. Myocardial preservation was maintained with cold blood cardioplegia and St. Thomas II crystalloid cardioplegia, and topical cooling. In all of the patients left internal mammary artery (LIMA)

and saphenous vein grafts were used as bypass conduits. No additional surgical procedure was done.

The two groups were similar in demographic data and aortic cross-clamp times (Table I). Postoperatively 5% dextrose and colloid (fresh frozen plasma and hydroxyethyl starch) solutions were infused to maintain the central venous pressure at 8-12 cm H₂O. Blood was transfused if the haematocrit fell below 25%.

Samples of arterial blood were taken to measure haematocrit, prothrombine and partial thromboplastin times (PT, PTT), and plasma fibrinogen levels, initially, after induction of anaesthesia; and at the end of operation and postoperative first day. PT, PTT and plasma fibrinogen levels were measured with a Amelung KCI coagulometer^d using Thromborel® packs for PTT and Fibro-Tec® packs^e for plasma fibrinogen levels.

Mediastinal drains were inserted before the closure of sternotomy and intermittent low-grade suction was applied postoperatively.

The raw data was entered into a data base program that followed the creation of graphic illustrations. Student's paired t test was performed to find out the analysis of variance.

Results

The mean age of the aprotinin treated group was 54.5 ± 5.1 years and the control group 52.9 ± 3.8 years, respectively. Total perfusion and the duration of aortic cross-clamp times were not statistically significant.

In group B, platelet numbers decreased significantly ($p < 0.05$) while rewarming (Fig.1.).

Table I. Comparison of the treatment and control groups.

	Aprotinin (n=30)	Control (n=30)	
Age (yr.)	52.9 (39-64)	54.5 (36-37)	NS
Weight (kg)	73 (61-83)	69 (60-80)	NS
Male/Female	4/26	5/25	NS
Total duration of CPB (min)	91 (62-132)	97 (58-162)	NS
Ischemic time (min)	49 (17-89)	45 (21-97)	NS
LIMA+distal anastomoses	87	92	NS

LIMA: Left internal mammary artery, NS: Not significant.

^a. Bayer AG, West Germany.

^b-Model BP-50, BIO-Medicus, Minnetonka, MN 55343.

^c-Cobe Laboratories, Inc, Lakewood, Co 80125.

^d-II. Amelung GMBH, West Germany.

^e. Behrinwerke AG, Margburg, West Germany.

	Hematocrit (%)	PT (sec)	PTT (sec)	Fibrinogen (mg/ml)	
Preop.					
Aprotinin	36.5	12.6±0.22	28.1±0.42	285±12	NS
Control	37.1	12.5±0.18	29.1±1.12	280±19	
Early-postop.					
Aprotinin	27.2*	18.6±0.8	26.2±0.5	245±19	NS
Control	24.5	17.8±0.6	23.7±0.4	250±17	
POD1					
Aprotinin	30.1	14.9±0.3	29.1±2.3	290±15	NS
Control	29.2	15.2±0.89	30.1±2.1	286±11	

POD1: Postoperative day 1, NS: not significant
* p<0.005

In contrast, aprotinin-treated patients maintained platelet count at a remarkably constant level throughout the CPB. After termination of CPB, a dramatic fall in platelet numbers occurred in both groups of patients. The decreased platelet counts during the early postoperative period, raised to their initial levels at the postoperative first day.

Hematologic and coagulation parameters are presented in Table II. There was no significance between PT, PTT and plasma fibrinogen levels, except hematocrit.

The measured blood drainage and blood transfusion among the two groups showed a significant difference ($p < 0.001$) (Fig. 2,3).

Discussion

Recent studies have been reported with using aprotinin for hemostasis following CPB. In these studies various effects of aprotinin have been investigated^{5,9,10}.

The most dramatic reductions in postoperative blood loss have been associated with the administration of aprotinin, an inhibitor of human trypsin, plasmin, and kallikrein. In low concentrations, aprotinin inhibits plasmin completely, thereby inhibiting

fibrinolysis⁵, although at very high concentrations, inhibition of kallikrein reduces blood coagulability. At intermediate concentrations, aprotinin inhibits platelet aggregation and activation, possibly by an effect on the platelet Von Willebrand, thrombin, and fibrinogen receptors^{6,7}. Aprotinin has been shown previously to reduce perioperative blood loss. In a dose of 200,000 KIU aprotinin reduced blood loss in patients undergoing transurethral resection of prostate⁶, probably as a result of reduced fibrinolysis. However, there was no effect on blood loss in open prostatectomy. In a recent study at higher doses (400,000 KIU), aprotinin was shown to reduce by an average of 21% the blood loss in cardiac surgery. It was stated that this effect occurred only if the drug was administered before the initiation of CPB⁸.

In this study a total dose of 1.5×10^6 KIU aprotinin was sufficient to reduce postoperative blood drainage when compared to the control group. This observation correlates with other study groups which have used a total amount of 3 to 5 million KIU of aprotinin⁹.

Reduced fibrinolysis by aprotinin may have a contribution to the decrease of blood drainage, but the main effect of this drug appears to be related directly or indirectly to

Fig.1. Platelet counts in both groups.

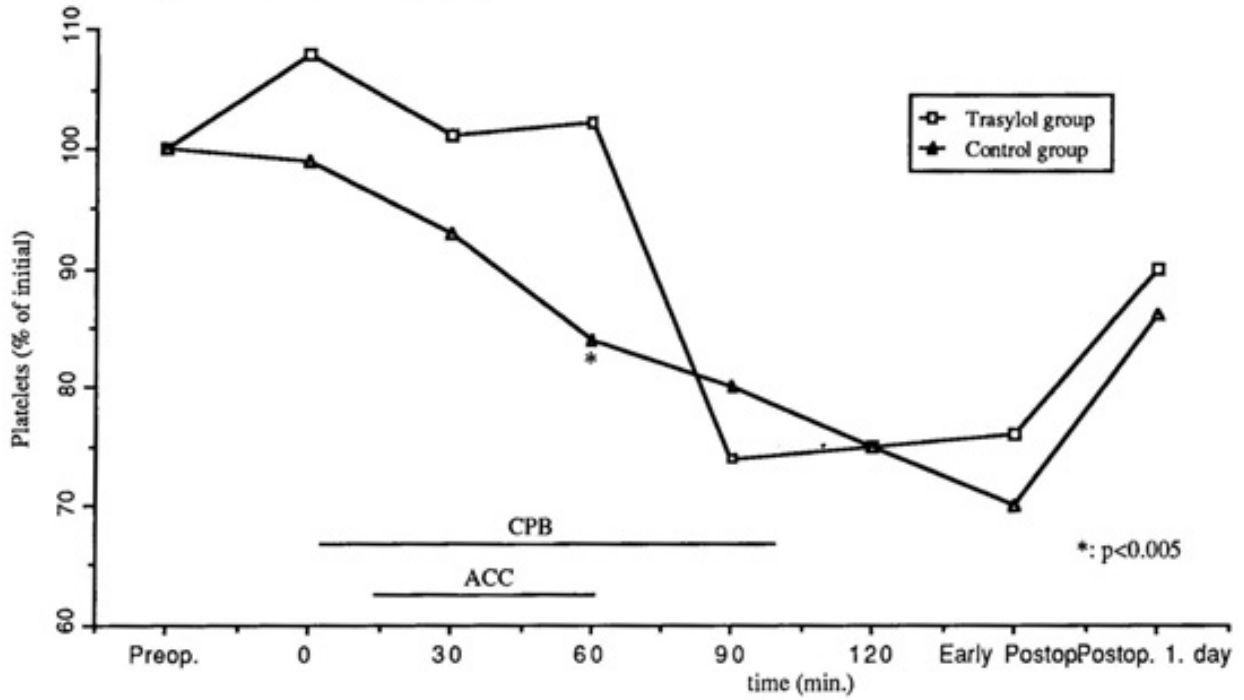


Fig.2. Postoperative drainage (ml)

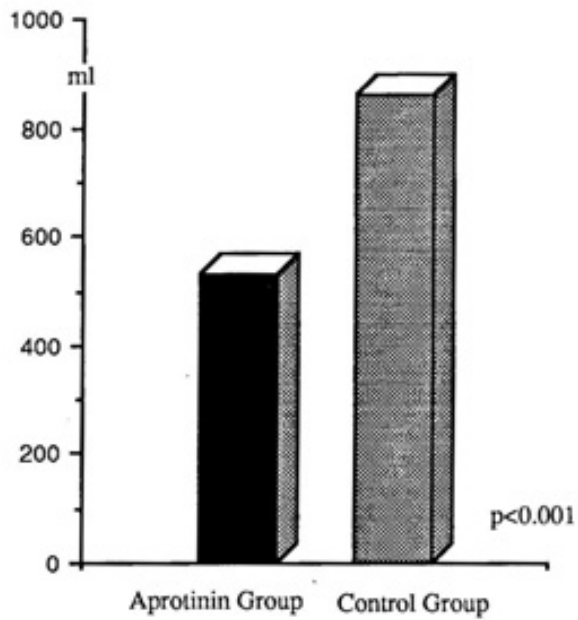
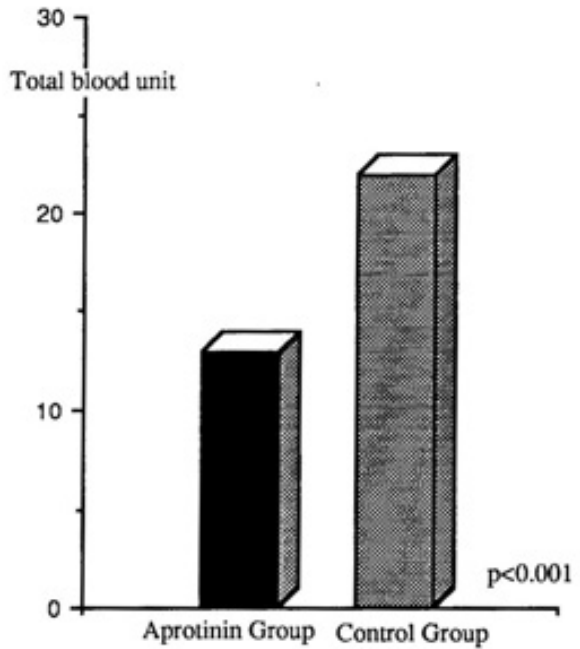


Fig.3. Postoperative blood usage (within 24 hr.)



platelet function. Desmopressin and epoprostenol has shown to effect the platelet functions like aprotinin¹⁰.

Aprotinin was claimed to be free of major adverse effects, but theoretically excessive doses might impair coagulation. There is also a possibility that improved coagulation with any of these drugs might increase the risks of arterial or deep venous thrombosis.

Based on our findings, we postulate that the deleterious effects of proteases on platelets, as exerted by plasmin, might be explained by their action on platelet receptors. Two main platelet receptors are to be considered; the Von Willebrand receptor for adhesion and the fibrinogen receptor for aggregation. The Von Willebrand receptor can be removed by plasmin⁷. The importance of Von Willebrand factor-platelet interaction during CPB was provided by Salzman and associates¹¹ who showed improved hemostasis after CPB by increasing the amount of endothelial Von Willebrand factor, which probably compensates for the decreased number of platelet receptors¹².

The fibrinogen receptor is exposed by a variety of platelet agonists such as adenosine diphosphate, thromboxane A₂, and proteolytic enzymes, all of which can be released during CPB¹³. Exposure of platelet receptors is accompanied by release of thromboxane A₂¹⁴. This causes platelet aggregation. Plasmin may remove the bound fibrinogen from platelets, thus preventing aggregation¹⁵, and resulting in ineffective postoperative platelet function. Evidence for loss of Von Willebrand and fibrinogen receptors during CPB is given by George and colleagues¹⁶.

Since aprotinin inhibits the release of thromboxane A₂, most likely the exposure of platelet receptors were effectively prevented in treated patients. This suggests that the impaired postoperative hemostasis in untreated patients has to be attributed to impaired platelet adhesion and platelet aggregation, where as aprotinin appears to have a protective effect on these specific platelet receptors. There was only a significant difference in platelet counts in both groups during the rewarming phase of operation.

Conclusion

We conclude that aprotinin infusion has important platelet-preserving effects during CPB, thus leading to a better hemostatic mechanism and consequently reducing postoperative blood loss and transfusion requirement.

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