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European Journal of Cardio-thoracic Surgery 20 (2001) 1122–1127

EUROPEAN JOURNAL OF CARDIO-THORACIC SURGERY

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Aprotinin reduces postoperative bleeding and the need for blood products in thoracic surgery: results of a randomized double-blind study ☆

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Received 14 June 2001; received in revised form 6 September 2001; accepted 25 September 2001

Abstract

Objective: Bleeding complications have been a major concern in certain thoracic surgery operations, especially decortication and pulmonary resection for inflammatory pulmonary infection. Prevention of plasminogen activation and fibrinolysis by aprotinin administration has been shown to reduce perioperative bleeding during operations associated with high blood consumption. **Methods**: Use of blood products (packed red cells, whole blood), chest tube drainage, analgesic requirement, chest tube duration for the patients undergoing major thoracic operations were recorded. In a double blind randomized fashion, patients were assigned to two groups receiving aprotinin ($n = 51$) at a loading dose of 10^6 kallikrein inhibitory units (KIU) followed by an infusion of the same dose during chest closure or receiving placebo ($n = 52$). On a daily basis, red-cell percentages of total fluid from drainage bottles were recorded and using the blood hematocrit level of the patient of the day before, the corrected value for the patient's blood volume equivalent of daily drainage was calculated. **Results**: There was a significant reduction in perioperative use of donor blood (0.98 ± 0.92 vs. 0.45 ± 0.32 unit; $P = 0.0026$), and total chest tube drainage (corrected value for the corresponding blood volume) (28.2 ± 36.9 vs. 76.9 ± 53.3 ml, $P = 0.0004$) (mean $\pm$ standard deviation) in the aprotinin group. However, aprotinin did not reduce postoperative transfusion or decrease in hematocrit level due to thoracic operations. In high transfusion-risk thoracic surgery patients (patients who underwent decortication, pulmonary resection for inflammatory lung disease and chest wall resection), the perioperative transfusion was only 0.50 ± 1.08 units in aprotinin group, compared with 1.94 ± 0.52 units in control group ($P = 0.003$). Postoperative transfusion was also reduced in aprotinin administrated group (0.53 ± 0.56 vs. 1.38 ± 0.97 units; $P = 0.02$). The mean total blood loss was decreased to nearly one third of the blood loss of the control group (41 ± 28 ml vs. 121 ± 68 ml; $P = 0.001$). **Conclusion**: Aprotinin significantly reduced perioperative transfusion requirement and postoperative bleeding during major thoracic operations. Aprotinin decreased perioperative transfusion needs. Moreover, patients who were at risk of greater blood loss during and after certain thoracic operations had a greater potential to benefit from prophylactic perioperative aprotinin treatment. © 2001 Elsevier Science B.V. All rights reserved.

Keywords: Thoracic surgery; Bleeding; Aprotinin; High transfusion risk surgery; Blood saving

1. Introduction

Bleeding during and after the certain thoracic operations remains a serious problem and the most common major complication in thoracic surgery. Re-exploration for hemorrhage is required in 3.7% of patients with case-fatality rates ranging from 17.8 to 38.4% [1]. Blood loss can be considerable during thoracic surgery especially for decortication, pneumonectomy, thoracic wall operations and operations for inflammatory pulmonary disease, empyema thoracis (i.e. decortication) [2–4]. One of the most appropriate approaches to blood conservation is to prevent blood loss at the time of surgery. Attention of the thoracic surgeon to careful hemostatic control may well save a patient from returning to theater for surgical re-exploration to find a bleeding point. However, there is a subset of patients in whom generalized oozing in the surgical field cannot be attributed to demonstrable bleeding vessels. There are no adequate definitions of an 'excessive bleeder' by means of laboratory or clinical parameters. Thus, using bleeding prevention agents might be taken into consideration. Several studies have demonstrated that aprotinin can reduce post- and perioperative bleeding and transfusion requirements associated with liver and lung transplantation, neurosurgery, vascular surgery and urological surgery as well as non-thoracic cardiac surgery [5–11]. The use of aprotinin for the prevention of hemorrhage in a patient with pulmonary aspergillosis and leukemia has been documented [12]. Our

☆ Presented as a preliminary report at the First International Congress of Thorax Surgery, Athens, Greece, July 1–8, 1997.

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PII: S1010-7940(01)01016-8

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objective is to investigate the role of aprotinin on bleeding during major thoracic surgery operations. We also aimed to document the possible effect of aprotinin on blood transfusion in a subset of thoracic operations such as thoracic wall resection, resection for inflammatory pulmonary/pleural diseases and pneumonectomy, which are usually defined as 'blood-demanding' operations. In an attempt to elucidate the effect of aprotinin on perioperative and postoperative oozing type hemorrhage, we evaluated blood requirement, and certain postoperative parameters in patients receiving aprotinin in a prospective, randomized double-blind trial.

2. Materials and methods

2.1. Patient population

One hundred and three patients undergoing major thoracic surgery operations were included in this study. Patients were randomized in a double-blind fashion into two groups; one group received placebo and the other received aprotinin. Exclusion criteria for enrollment in the study included known or suspected allergy to aprotinin, a serum creatinine level greater than 2 mg/dl, presence of hemorrhagic diathesis or known coagulation factor deficiency and intake of oral contraceptives, pre-existing coagulation defects (platelet count $< 150 \times 10^9$/l, prothrombin time (PT) or partial prothrombin time (PTT) $> 1.5\times$ control value). The randomization was done by the nurse who prepared the sachets containing either aprotinin or only vehicle (5% dextrose). Each patient was randomly assigned a number and then given the corresponding sachets. Only the aforementioned nurse was privy to the assignments. After the study was completed, the randomization code was broken and the data were statistically analyzed. One-hundred and three patients consisting of 51 patients who received aprotinin (aprotinin group) and 52 patients who received placebo (control group) were analyzed. All procedures were performed by the same surgical team through a posterolateral thoracotomy at the fifth or sixth intercostal space. No patient was given heparin during or after operations. Patients experiencing accidental intermediate venous or arterial hemorrhage (i.e. main pulmonary artery, veins or their explored branches) were excluded from the study. Performed operations in aprotinin and control groups are documented in Table 1. In all patients, either a 32-F or 28-F chest tube was positioned anteriorly and a 36-F one was positioned posteriorly. All of the patients were transferred to the intensive care unit (ICU) following operation. During the postoperative period, chest tubes were placed on-20–25 cmH_2O suction and were removed when no air leak was evident and when the drainage was less than 150 ml in 24 h.

Table 1
Patients' demographic data[a] (mean ± SEM)

	Aprotinin	Control
Gender (M/F)	47:4	45:7
Age (years)	54.6 (4.1)	50.3 (5.2)
Initial hematocrit level (%)	40.6 (1.1)	40.3 (0.9)
Initial platelet count (10^3/μl)	233 (19)	224 (28)
Serum creatinine (mg/dl)	0.92 (0.11)	0.82 (0.23)
Operation		
Lobectomy	13	12
Pneumonectomy	9	11
Bilobectomy	3	3
Decortication	8	5
Operations for hydatid cyst	7	10
Bullectomy	8	7
Other	3	4

[a] No statistically significant difference was found between the study groups.

2.2. Dosage of aprotinin

Patients in the aprotinin group received 1×10^6 kallikrein inhibitory units (KIU) aprotinin (Trasylol; Bayer AG, Leverkusen, Germany) given in 100 ml 5% dextrose solution after induction of anesthesia, and the same dose was administered intravenously while approximating the ribs (at the beginning of the closing of thoracotomy). No test dose was given to any patient before operations.

2.3. Blood transfusion protocol

During the operations the patients were routinely given 1000 ml/h lactated Ringer's solution. The indications for perioperative whole blood or packed erythrocyte suspension were the presence of excessive active bleeding (>200 ml/h) or unpreventable systolic blood pressure decrease despite of Ringer's solution infusion below 90 mmHg. No autotransfusion was done during or after the operations.

2.4. Postoperative care

In our institution during the postoperative period, pethidine chloride, a synthetic morphine analogue, was used as narcotic analgesic via subcutaneous or intramuscular route at a dose of 30 mg for each administration when the patient noticed a strong pain despite the routinely administered non-steroid analgesic agent (metamisole). Metamisole was administered twice for the first postoperative 12 h intravenously at a dose of 200 mg and was given 2 g orally per day until the day upon which the last chest tube was removed. Blood loss from the chest tubes was recorded daily from the time the patient arrived in the ICU.

2.5. Drainage calculation

Due to the non-hemorrhagic serous component of thoracic drainage, amount of tube drainage itself was not thought to be appropriate for the evaluation of blood loss from thoracic cavity. Therefore, every morning, red-cell percentages of shaken and homogenized fluid from drainage bottles were recorded and using the blood hematocrit level

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of the patient of the day before, the corrected value for the patient's blood volume equivalent of daily drainage was calculated and recorded. Postoperatively, patients with hematocrit levels less than 30% were transfused until the hematocrit level rose above 30%.

The study has been approved and certified to be appropriate by the ethical committee of the hospital.

2.6. Statistical analysis

Data are reported as mean ± standard error of mean (SEM) or as a number (percentage). SPSS software for Power Macintosh computers was used on a personal Apple computer for statistics. The Student's *t*-test was used as test for statistical significance of normally distributed values. A Mann–Whitney *U* rank sum test or chi-square test (number of operations, sex comparison) were used for non-parametric values. If the *P*-value was less than 0.05, the result was considered to be significant.

3. Results

The patients ranged in age from 12 to 79 years (54.6 ± 4.1 (SEM)) in the aprotinin group and from 18 to 70 years (50.3 ± 5.2) in the control group. Characteristics of the patients and type of performed operations are shown in Table 1. There were no differences between treatment groups with respect to age, gender, hematocrit, serum creatinine levels and performed operations. The difference in hematocrit levels between the preoperative and postoperative fourth or fifth day was found to be lowered from 5.50 ± 0.50% in the control group to 3.52 ± 0.71% in the aprotinin group, although the difference was not found to be statistically significant ($P = 0.22$).

The mean number of given units of blood product during operations was 0.98 ± 0.13 unit in the control group and only 0.45 ± 0.08 unit in the aprotinin group ($P = 0.0026$; Fig. 1). However, during the postoperative course, aprotinin did not reduce the number of blood transfusions in a statistically significant manner (means were 0.18 ± 0.06 unit in the control group and 0.12 ± 0.016 unit in the aprotinin group; $P = 0.32$; Fig. 1). We found that the blood volume equivalent of total chest tube drainage (as described in Section 2) was 28.2 ± 5.2 ml in the aprotinin group compared with 76.9 ± 7.4 ml in control group (Fig. 2; $P = 0.0004$).

The total narcotic analgesic requirement during the postoperative course was also marginally lower in the aprotinin group (325 ± 33 vs. 487 ± 28 mg), but the difference was not found to be statistically significant ($P = 0.13$). The difference between ICU stay of patients, and removal day of tube thoracotomies, were found not to be statistically significant (data not shown).

Thirty patients out of 103 underwent more blood-demanding procedures such as decortication ($n = 13$), chest wall resection due to tumor invasion ($n = 6$), pneumonectomy for pleuropulmonary infection ($n = 6$), and lobectomy for pleuropulmonary infection ($n = 5$). In those patients, 16 had been randomized to the aprotinin group and another 14 to the control group. There was no difference

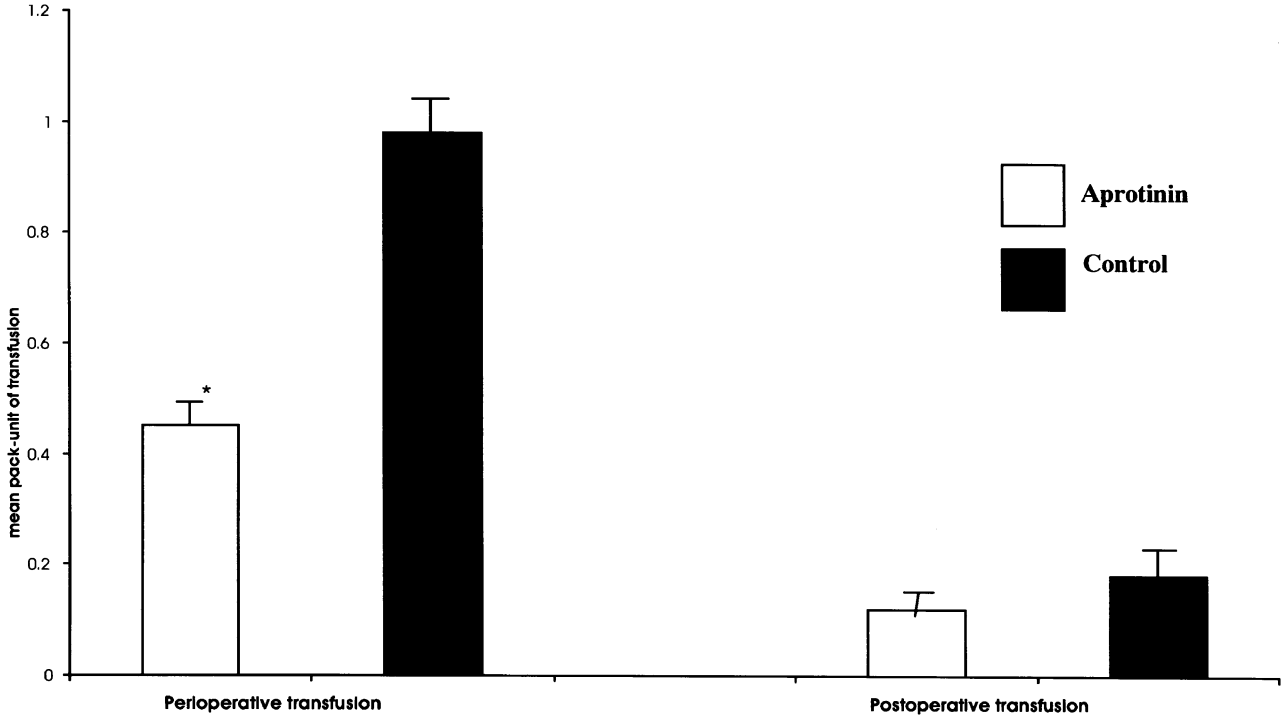

Fig. 1. Effect of aprotinin on perioperative and postoperative mean blood transfusion in all patients. *$P = 0.0026$.

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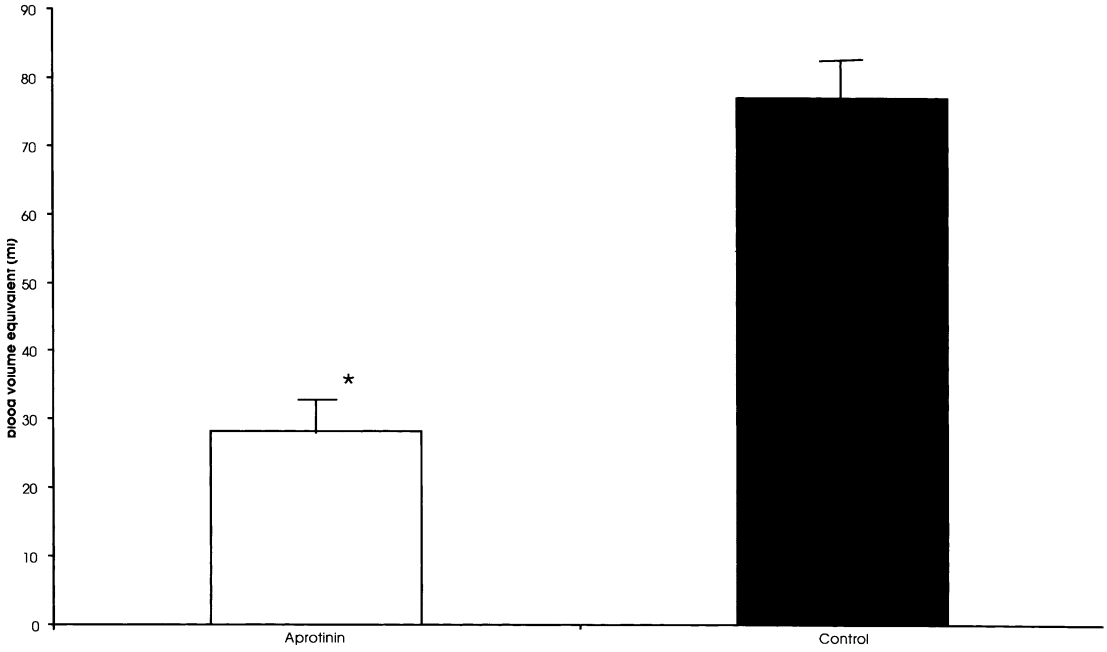

Fig. 2. Blood volume equivalent of total chest tube drainage in all patients. *$P = 0.0004$.

between the aprotinin and control groups with respect to clinical characteristics. In those 30 patients, the effect of aprotinin in perioperative, postoperative blood transfusion and postoperative blood loss were found to be more prominent between the aprotinin and the placebo group (Table 2; $P = 0.007$, $P < 0.01$, $P < 0.005$). Additionally, the mean hospital stay decreased from 9.4 ± 1.2 to 6.5 ± 0.8 days in the aprotinin group ($P = 0.002$). ICU stay of the aprotinin group was reduced compared with that of the control group (from 4.4 ± 0.4 to 2.1 ± 0.5 days; $P = 0.007$). There also appeared to be a significant difference, favoring aprotinin, in the duration of chest tube drainage, 2.6 ± 1.1 vs. 1.4 ± 0.3 days ($P = 0.009$).

4. Discussion

A thoracic surgery operation may complicate with perioperative and/or postoperative hemorrhage which is associated with the need for transfusions and additional surgical procedures.

Aprotinin, a serine protease inhibitor, is a polypeptide consisting of 58 amino acid residues with a molecular weight of 6512 Da, whose method of action remains elusive [5]. It preserves fibrinogen levels [13], prevents the platelet adhesive receptor (GPIb) from degradation and reduces thromboxane A_2 release [5]. It has been also reported that aprotinin shows its protective effect via preserving GP IIb–IIIa receptor function [14,15]. It could possibly decrease expression of fibrinogen binding [16]. Aprotinin has been used extensively in patients undergoing cardiac operations in an effort to minimize perioperative blood loss and prevent the potential complications associated with blood transfusions and re-operations for the control of bleeding [6,8,11,14]. Also it has been shown that aprotinin reduced the need for blood products during liver transplantation [8], neurosurgery [9], urological surgery [10], and diminished the bleeding of patients with pulmonary aspergillosis and leukemia [11].

Table 2
Blood loss[a] in blood demanding procedures

Parameter	Aprotinin	Control	*P*
Perioperative transfusion (units)	0.50 (0.27)	1.94 (0.14)	0.003
Postoperative transfusion (units)	0.53 (0.14)	1.38 (0.26)	0.02
Postoperative blood loss (ml)	41.3 (7.1)	121.6 (18.5)	0.001
Mean postoperative hematocrit (%)	35.2 (4.6)	36.3 (2.5)	0.87

[a] Values are mean (SEM).

We evaluated the effect of aprotinin in patients undergoing major thoracic surgery operations that are associated with a considerable risk of bleeding. As seen in the study, aprotinin significantly reduced the postoperative bleeding as measured by means of blood volume equivalent of total thoracic drainage. Aprotinin also caused a significant reduction in perioperative blood transfusion. Although aprotinin seemed to recover the postoperative decrease in the hematocrit level, the difference was not found to be statistically significant. Since patients with intraoperative accidental venous or arterial hemorrhage were excluded from the study, the effect of aprotinin was thought to be directed to oozing-type hemorrhage during or after the operations.

For perioperative blood loss, the difference of the mean

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1.44 units seen in high-transfusion-risk thoracic surgery patients is more clinically relevant than the 0.58 unit recorded in all patients of our study.

It was reported that platelet dysfunction is considered to be the most frequent cause of blood loss after cardiothoracic surgery [17]. Although the mechanism of the reported beneficial effect of aprotinin has not been investigated in non-cardiac thoracic surgery, it appears that a platelet-protective effect during thoracic surgery may play a role. It was also published that aprotinin preserved the functional receptor GPIIb–IIIA, which is mainly responsible for platelet aggregation [5,11,15].

We also demonstrated that patients potentially susceptible to hemorrhage during and after thoracic operations such as decortication for empyema thoracic with or without tuberculosis, thoracic wall resection due to tumor invasion to thoracic wall, and pneumonectomy for inflammatory pulmonary diseases mostly benefited from aprotinin administration. Having known that operations in those patients may lead to intraoperative oozing-type bleeding probably due to dense adhesions between lung and thoracic wall [18], saving the platelet function using the effect of aprotinin might have a preventive role in such patients.

We have also demonstrated that aprotinin slightly reduced the patient's additional need for narcotic analgesia during the first 3–5 days after operation, but this reduction was not found to be statistically significant. Although the value of that finding is limited since we did not measure the pain intensity of the patients by means of any standardized pain scoring method, there is a theoretical possibility of an analgesic effect of aprotinin since aprotinin as a non-specific serine antiprotease blocks the kallikrein-to-kinin conversion [5] and kinins are among the most important pain-inducing substances produced in various tissues. It was also shown that aprotinin reduces nitric oxide production, which may indicate an inflammation- and pain-modifying effect through a different mechanism of action [19]. However, although the possible effect of aprotinin on narcotic usage was considered in this study, its use as an analgesic agent could not be justified. The possible effect is only of importance in order to give insight for investigating the modus operandi of pain-generating mechanisms. A study with larger series might clarify this analgesic effect. We demonstrated no difference in the monitoring period of patients in the ICU, suggesting that aprotinin had no benefit on overall hemodynamic and oxygenation status of patients, which were decisive factors for patients' stay at the ICU (data not shown). It must be emphasized that a shortened stay at the ICU has yet to be attributed to the effect of aprotinin administration.

However, an analysis of 30 patients who have high risk for bleeding and who underwent decortication, chest wall resection due to tumor invasion, pneumonectomy for pleuropulmonary infection, and lobectomy for pleuropulmonary infection showed that the blood-saving effect of aprotinin during and after thoracic operation was found to be more prominent and statistically significant (Table 2). Postoperative blood loss decreased to one third that of the control patients (Table 2). This effect appears to be consistent with the platelet-preserving effect of aprotinin which seems to be the result of preservation of efficient blood plugs. The importance of blood plugs is the prevention of oozing-type bleeding from the multiple hemorrhagic sites formed by parietal pleural or thoracic-wall injury.

The adverse effects of aprotinin have been well documented and reported to be almost limited to allergic reactions in less than 0.1% [5]. We observed no allergic reaction in patients, probably due to the fact that no patient had been given aprotinin before. We observed no other considerable side effect of aprotinin in this study.

Recently, Kyriss et al. reported the blood-saving effect of aprotinin in thoracic surgery interventions associated with an increased risk of bleeding due to inflammatory conditions which were similarly seen in our patients [20]. In that study, a different dose of aprotinin (2×10^6 KIU) and an infusion (5×10^5 KIU/h) were used. In our study, we showed the efficacy of aprotinin in intraoperative and postoperative blood loss, and ICU and hospital stay in general elective surgery patients not only with inflammatory, but also with non-inflammatory conditions. By using blood-equivalent of chest-tube drainage as a parameter. we additionally documented the real hemorrhage-diminishing effect of aprotinin.

In our trial, we were unable to measure the local (thoracic cavity) or generalized effects of aprotinin such as the reduction of D-dimer production, thrombin–antithrombin complex, and the promotion of fibrin formation which might be speculated to play some role in reducing the blood loss during thoracic surgery.

In summary, aprotinin reduces perioperative blood loss and the need for blood products during major thoracic surgery operations. Although a routine use of aprotinin in all thoracic operations is yet to be justified, patients who are at risk of greater blood loss during and after certain procedures have a greater potential to benefit from prophylactic aprotinin treatment. Further studies to clarify the effect and unveil the mechanism of its action are warranted.

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