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The Critical Role of Aprotinin in Controlling Haemostasis in Conjunction with Non-Pharmacological Blood-Saving Strategies During Routine Coronary Artery Bypass Surgery

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Abstract

Objective: Aprotinin, a non-specific serine protease inhibitor, has been confirmed to be safe and effective in reducing intra- and postoperative blood drainage, transfusion requirements, and perioperative morbidity and mortality during coronary artery bypass surgery. It is the only one of the currently available haemostatic agents that is approved by the U.S. Food and Drug Administration (FDA) for use in cardiac surgery. However, one major weakness of currently available trials is the lack of information regarding the concomitant usage of aprotinin with blood-saving strategies that have been used more frequently in recent years.

Methods: Patients undergoing elective first-time coronary artery bypass grafting (n = 172) who were given systemic high-dose aprotinin (n = 85), combined systemic high-dose aprotinin and topical aprotinin (n = 27), or no aprotinin (n = 60) were reviewed retrospectively. The use of all blood-saving procedures was systematically taken in account.

Results: Postoperative blood drainage was significantly less in patients treated with aprotinin than controls ($P < 0.0001$). Concomitant use of topical aprotinin was accompanied by a postoperative blood loss reduction of 35% compared to systemic aprotinin use alone ($P < 0.003$). The intra- and postoperative donor blood requirements were dramatically reduced in both aprotinin-treated groups compared to controls, although patients received different blood saving strategies as appropriate ($P < 0.0001$). A trend of up to 20% lower postoperative blood drainage was noted in patients in whom intraoperative haemodilution and autologuos blood transfusions were used ($P > 0.05$).

Conclusions: The present analysis demonstrates that the local and systemic administration of aprotinin is safe and effective in reducing intra- and postoperative blood drainage and transfusion requirements. In elective CABG procedures, aprotinin should still be used even if blood-saving strategies are employed.

Key words: Surgery, Cardiovascular, Coronary artery, Extracorporeal circulation, Blood loss, Kallikrein inhibitor, Aprotinin

1. Introduction

Excessive postoperative blood loss is one of the major risks for patients undergoing cardiovascular surgery that involves cardiopulmonary bypass (CBP) [1-3]. The mechanical trauma caused by contact between blood and the foreign surface of the CPB circuit is associated with the induction of a transient haemostatic defect that appears to be related to various factors that control normal haemostasis. In particular, complement activation by the kallikrein-kinin-system, platelet dysfunction caused by reduced surface expression of glycoproteins Ib, IIb-IIIa, and the activation of plasmin-mediated fibrinolysis have been found to be affected [4-8]. The haemostatic defect results in an increased risk for blood product transfusion and the need for surgical re-exploration, which substantially contributes to postoperative morbidity and mortality after cardiac surgery [3]. Aprotinin, a non-specific serine protease inhibitor, has been recognized for many years as a haemostatic agent that is useful in cardiac surgery [9]. Meta-analyses of controlled clinical trials have confirmed that the prophylactic intravenous administration of aprotinin not only reduces blood loss, but also reduces transfusion requirements, the frequency of surgical re-exploration for bleeding, and overall mortality [2, 10, 11]. The evidence suggests that the haemostatic effects of aprotinin are primarily based on its platelet preserving function and the inhibition of plasmin- and kallikrein-mediated fibrinolysis [12-17]. In recent years, several approaches have been investigated to decrease postoperative blood loss and, thereby, transfusion requirements. The use of high-dose intravenous aprotinin has been shown to be the most effective among the various pharmacological intervention strategies that are used in cardiac surgery in terms of decreases in blood loss, transfusion requirements, and overall mortality [18, 19]. However, the aprotinin dose regimen and its mode of application is still a subject of controversy due to concerns that have been raised about an increased risk of cardiovascular, cerebrovascular, and renal events, as well as the high cost of aprotinin [20-26]. Approaches to minimize these concerns that have focused on dose reduction and the time point when aprotinin was ad-

ministered during surgery have been found to less effective [22, 23, 25]. In contrast, non-pharmacological blood-saving strategies, such as intraoperative haemodilution and autologous blood transfusions, the use of cell-saver systems, and blood-saving surgical techniques have been proven to reduce postoperative blood drainage, and their use has been steadily increasing in recent years [27-31]. However, on reviewing the recent literature, one major weakness that may distort the results was found: most studies do not report on the frequency of using the various cell-saving strategies. Thus, the benefit of intraoperative aprotinin has not been clearly demonstrated in the literature. Therefore, we decided to analyse whether, after two decades of routine use and taking different intraoperative blood saving strategies during surgery into account, systemic and topical aprotinin still offers an advantage with respect to postoperative blood loss and transfusion requirements in comparison to non-aprotinin-treated patients undergoing elective coronary artery bypass grafting (CABG). Moreover, we analyzed the impact of the various blood-saving strategies on postoperative blood drainage.

2. Methods

2.1. Patients Selection

We retrospectively reviewed the records of consecutive male and female patients undergoing elective first-time coronary artery bypass surgery using extracorporeal circulation (ECC) over the course of six month in our department. Urgent patients, off-pump procedures, and complex cardiac surgery procedures other than bypass grafting were excluded. Patients with documented intraoperative surgical complications and operations > 6 h duration were excluded from further analyses. Patients treated with the different intraoperative aprotinin regimens that were used at our institution were included, but patients treated with other pharmacological haemostatic agents other than aprotinin were excluded. The internal mammary artery was dissected for bypass grafting in all patients. Patients between 40-85 years of age having an ejection fraction of ≥ 30% were included. However, patients who had undergone interventional cardiological procedures within three months of surgery were not included. Also excluded from the analysis were patients: with a bleeding disorder; receiving aspirin or any other anticoagulant within one week prior to surgery; suffering from a hepatic synthesis disturbance, a tumor, or with renal failure requiring dialysis and a preoperative serum creatinine level of > 2.0 mg/dl. All criteria had to be satisfied on patient chart review. Patients who were treated with intraoperative blood-saving strategies, such as intraoperative haemodilution and autologuos blood transfusions, as well as cell-saver systems, were included. Informed consent was obtained from each patient in conformity with the Declaration of Helsinki.

2.2. Aprotinin Dosage Protocols

Patients were included if they received (i) high-dose aprotinin systemically (Trasylol®, Bayer Vital GmbH & Co. KG, Leverkusen, Germany) based on body weight. Briefly, the dosing consists of a loading dose of 30,000 KIU (kallikrein inhibitor units)/kg body weight before the start of CPB, with the same amount added to the priming volume. This is followed by a continuous infusion of 130 KIU/kg/min until neutralization of heparin with protamine. We included patients who received topical aprotinin during surgery in addition to the described weight-related systemic high-dose regimen (ii). Topical aprotinin was applied in a dosage of 1.0×10^6 KIU into the pericardial cavity and onto the thoracic wound surface after resuming CPB during chest closure. Finally, patients receiving neither systemic nor topical aprotinin during surgery who met the inclusion and exclusion criteria (iii) were included.

2.3. Data Extraction Criteria

The outcomes that were measured included: the amount of postoperative blood loss; the number of patients receiving blood and blood product transfusions and the amount of blood and blood product transfusion used; perioperative renal function; non-fatal myocardial infarction; stroke; thrombosis; embolism; and mortality. Patients were considered for inclusion if their charts had complete data with respect to the study selection criteria.

In general, postoperative blood loss was determined after wound closure and continuous suction (-15 cm H_2O) was applied to the chest drains in the operating room until removal of the drains. Before chest closure, all residual fluids were suctioned from the pericardial cavity and the left pleural space that had been opened during preparation of the left internal mammary artery, and the lungs were hyperinflated for a short period of time. At the end of surgery, we generally inserted two drains, a left pleural drain and a pericardial drain, in each patient. The drains were removed when the drain fluid became serous. The total blood drainage was noted in the flowcharts. Patients with a blood loss > 500 ml/h within the first 6 h postoperatively required re-thoracotomy, as a surgical cause of bleeding was assumed; such patients were excluded from further evaluation. Banked donor blood was transfused at a hematocrit level < 20% during ECC and at a haemoglobin level < 9.0 g/l postoperatively. Patients who were transfused with cell-saver blood were included, but patients transfused with shed mediastinal blood were excluded from further analyses. Transfusion of fresh frozen plasma (FFP) was given if the patient had an abnormal prothrombin time and depended on the amount of bleeding. The platelet transfusion threshold was set at a platelet count of ≤ 50/nl with associated increased blood loss. Myocardial infarction was diagnosed by standard 12-lead electrocardiogram (ECG) and the routine determination of cardiac specific serum markers. Clinically suspected strokes and embolism were confirmed by computer tomography scan, and clinically suspected peripheral thrombosis was investigated by duplex ultrasound.

2.4. Standardized Surgical Procedure, Anaesthesia, and CPB

The patients reviewed had standardised anaesthesia and cannulation for extracorporeal circulation. Anaes-

thesia was routinely induced and maintained with fentanyl, etomidate, and pancuronium bromide. The CPB circuit was primed in a standard manner with 2.0 l Ringers-lactate-solution, 100 ml 20% mannitol, 12.5 mEq sodium bicarbonate, 10 ml 20% glucose, and 2,500 IU sodium heparin. The target hematocrit value during extracorporal perfusion was 22%. Systemic anticoagulation was established using heparin (300 IU/kg) given before cannulation of the aorta and frequently monitored by the activated coagulation time (ACT) with a kaolin-activated Hemochron device (International Technidyne Corp, Edison, USA). The target ACT during CPB was > 450 sec. Moderate hypothermia at 30 °C, cold crystalloid cardioplegia (Eppendorf, Hamburg, Germany), and topical myocardial cooling with ice slush were used for myocardial protection. During hypothermia, the pump flow was reduced to 2.0 l/min/m^2. Finally, heparin was neutralized with protamine sulfate in a 1:1 ratio after CPB discontinuation.

2.5. Statistical Evaluation

Analyses and preparation of the figures were performed with the Statistical Package for the Social Science (SPSS, version 10.1, USA) and the Software for Scientific Graphing (Origin, version 6.1, USA). Data are expressed as mean ± standard deviation (SD); n refers to the sample size. The means between groups were compared using the unpaired Student's t-test, and, where necessary, an ANOVA test was used for multiple comparisons. A two-sided test at an α-level < 0.05 was considered statistically significant.

3. Results

We identified 172 patients who met the inclusion criteria. All patients had a first-time elective CABG, and at least one internal mammary artery was dissected for bypass grafting. In all patients, any oral anticoagulant drugs were discontinued 7 days before surgery, and the coagulation levels and blood counts were within normal limits prior to surgery. The cardiac ejection fraction was > 30% in all study patients. The patients were divided into 3 treatment groups: Group I patients (n = 27), who received combined systemic high-dose aprotinin and topical aprotinin into the thoracic cavity and onto the wound surface; Group II (n = 85), who received only systemic high-dose aprotinin intravenously; and Group III (n = 60), who received neither systemic nor topical aprotinin.

3.1. Demographic and Operative Features

Except for gender, the patients were well matched with respect to their demographic features; females were underrepresented in all groups (18.6%). The mean age ranged from 63-65 years, the mean body weight ranged from 77-81 kg, and the mean height ranged from 171-172 cm (Table 1: A). There were no differences among the groups with respect to the mean number of proximal and distal anastomoses (all P > 0.05); the number of proximal anastomoses ranged from 1-4, and the number of distal anastomoses ranged from 1-6 (Table 1: B). The intraoperative use of aprotinin was not associated with significantly shorter mean operative and ECC-times (Group I, 105; Group II, 93; and Group III, 106 min, all P > 0.05) as detailed in Table 1: B. The mean systemic aprotinin dose did not differ between the two groups given aprotinin (P > 0.05, Table 1: C). In all 3 groups, after ECC was resumed, heparin was neutralized in a 1:1 ratio followed by repeated measurements of the ACT, which returned to the normal range before the patients left the operating room (data not shown).

3.2. Intraoperative Blood-saving Strategies and Postoperative Blood Loss

Overall, intraoperative haemodilution and autologuos blood transfusions were done in 30%-45% of the patients. Blood that accumulated in the ECC system was retransfused after resuming ECC in almost all patients, while cell-saver systems were rarely used (Table 2). Postoperative blood loss was recorded from the end of surgery after a short period of lung hyperinflation, which was done to ensure that no residual intrapleural fluid remained, until removal of the drains. Patients treated with topical aprotinin in addition to intravenous high-dose aprotinin (Group I) during surgery had the lowest mean postoperative blood loss, while the patients receiving no aprotinin (Group III) had the highest postoperative blood drainage. In particular, Group I patients had a 35% decrease in the mean total postoperative blood drainage compared to Group II patients (Group I, 374 ± 122 ml vs. Group II, 576 ± 220 ml, P < 0.003), and the mean total blood loss in Group III was about 50%-70% higher than for Groups I and II (1201 ± 585 ml, P < 0.0001) (Figure 1a and b). There was a trend towards lower postoperative blood drainage (up to 20%) in patients in whom intraoperative haemodilution and autologous blood transfusions were done, but this trend was not statistically significant (P > 0.05).

3.3. Intra- and Postoperative Transfusion of Blood and Blood Products

The significant blood loss reduction that was noted in patients receiving topical aprotinin in addition to systemic high-dose aprotinin (Group I) did not reduce postoperative packed red blood cell transfusion compared to Group II patients who received only systemic high-dose aprotinin (Group I, 0.6 U and Group II, 0.6 U). However, the mean intra- and postoperative need for banked donor blood was significantly reduced in Group I and II patients compared to patients who were not given aprotinin treatment (Group III, 2.3 U, P < 0.001) (Table 3).

3.4. Complications and Safety of Aprotinin

A test-dose of aprotinin (1.0 x 10^4 KIU) was given intravenously after the induction of anaesthesia to assess the potential for allergic reactions. No allergies to aprotinin were seen in any aprotinin-treated patients. No evidence of perioperative myocardial infarction was seen in Group I-III patients based on electro-

Table 1. Demographic and operative features. Group I patients received a weight-related systemic high-dose aprotinin regimen and topical aprotinin applied in a dosage of 1.0 x 10^6 KIU into the pericardial cavity and onto the thoracic wound surface after resuming CPB during chest closure. Group II patients received a weight-related systemic high-dose aprotinin regimen only. Group III patients received neither systemic nor topical aprotinin during surgery.

	Groups			P value
	I	II	III	
A: Demographic features				
Patients (n)	27	85	60	
Gender				
Male	22	67	51	
Female	5	18	9	
Age (y)	63.0 ± 9.0	65.0 ± 9.0	64.0 ± 9.0	ns
Range (y)	48.0 – 75.0	40.0 – 84.0	42.0 – 76.0	
Body weight (kg)	77.0 ± 12.0	81.0 ± 12.0	77.0 ± 11.0	ns
Range (kg)	68.0 – 115	55.0 – 114	59.0 – 105	
Body size (cm)	170 ± 8.0	172 ± 7.0	171 ± 8.0	ns
Range (cm)	149 – 183	155 – 185	154 – 189	
B: Operative features				
Op-time (min)	215 ± 28	199 ± 44	226 ± 39	ns
Range (min)	165 – 270	115 – 360	144 – 340	
ECC-time (min)	105 ± 23.0	93 ± 27.0	106 ± 22.0	ns
Range (min)	73.0 – 171	48.0 – 207	45.0 – 153	
No. of proximal anastomosis	2.3 ± 0.7	2.2 ± 0.6	2.4 ± 0.9	ns
Range	1 – 3	1 – 3	0 – 4	
No. of distal anastomosis	3.3 ± 0.7	3.1 ± 0.7	3.5 ± 0.8	ns
Range	2 – 4	1 – 4	2 – 6	
C: Drug dosages				
Aprotinin bolus (x 10^6 KIU)	2.3 ± 0.4	2.4 ± 0.4		ns
Range (x 10^6 KIU)	2.0 – 3.0	2.0 – 3.0		
Aprotinin priming (x 10^6 KIU)	2.3 ± 0.4	2.4 ± 0.4		ns
Range (x 10^6 KIU)	2.0 – 3.0	2.0 – 3.0		
Aprotinin infusion duration (min)	150 ± 27.0	141 ± 31.0		ns
Range (min)	114 – 214	82.0 – 299		
Heparin total dose (10^3 U)	36.0 ± 7.0	36.0 ± 7.0	35.0 ± 6.0	ns
Range (10^3 U)	27.0 – 59.0	27.0 – 55.0	26.0 – 54.0	
Protamine total dose (10^3 U)	31.0 ± 7.0	32.0 ± 7.0	33.0 ± 7.0	ns
Range (10^3 U)	19.0 – 45.0	20.0 – 50.0	22.0 – 52.0	

Data are expressed as mean ± standard deviation and minimum - maximum, n refers to the number of patients, KIU (kallikrein inhibitor units), U (Units), ns (not significant for comparison between groups)

cardiography and routine serial measurement of cardiospecific serum enzymes. Furthermore, no patients developed deep vein thrombosis, pulmonary embolism, or renal failure requiring dialysis. However, a moderate, but not significant, reversible increase in serum creatinine was observed; a creatinine increase of 0.5-1.0 mg/dl occurred in 2 Group I patients, 3 Group II patients, and 3 Group III patients, while a serum creatinine increase of 1.1-1.5 mg/dl was only seen in 4 Group II patients.

4. Discussion

For almost two decades, various aprotinin regimens have been frequently used in cardiac surgery involving CPB [9]. However, the optimal dose regimen and its mode of application have not yet been determined. We recently reported that the more pronounced fibrinolytic activity in the pericardial cavity than in the systemic circulation that occurs after CPB could be substantially decreased by aprotinin applied topically [32].

Table 2. Perioperative blood saving strategies. Group I patients received a weight-related systemic high-dose aprotinin regimen and topical aprotinin applied in a dosage of 1.0 x 10^6 KIU into the pericardial cavity and onto the thoracic wound surface after resuming CPB during chest closure. Group II patients received a weight-related systemic high-dose aprotinin regimen only. Group III patients received neither systemic nor topical aprotinin during surgery.

	Groups			P value
	I	II	III	
A: Autologous blood transfusion				
(n)	8 (27)	38 (85)	27 (60)	
Volume (ml)	242 ± 420	344 ± 390	357 ± 483	ns
Range (ml)	0 – 1,300	0 – 1,200	0 – 1,300	
B: Retranfusion of ECC blood				
(n)	26 (27)	77 (86)	57 (60)	
Volume (ml)	713 ± 257	647 ± 316	653 ± 322	ns
Range (ml)	0 – 1,200	0 – 1,200	0 – 1,400	
C: Retranfusion of CS blood				
(n)	1 (27)	6 (86)	3 (60)	
Volume (ml)	26 ± 135	71 ± 239	34 ± 184	ns
Range (ml)	0 – 700	0 – 1,120	0 – 1,070	

Data are expressed as mean ± standard deviation and minimum - maximum, n refers to the number of patients receiving the named cell-saving strategy, in brackets total number of patients, ns (not significant for comparison between groups)

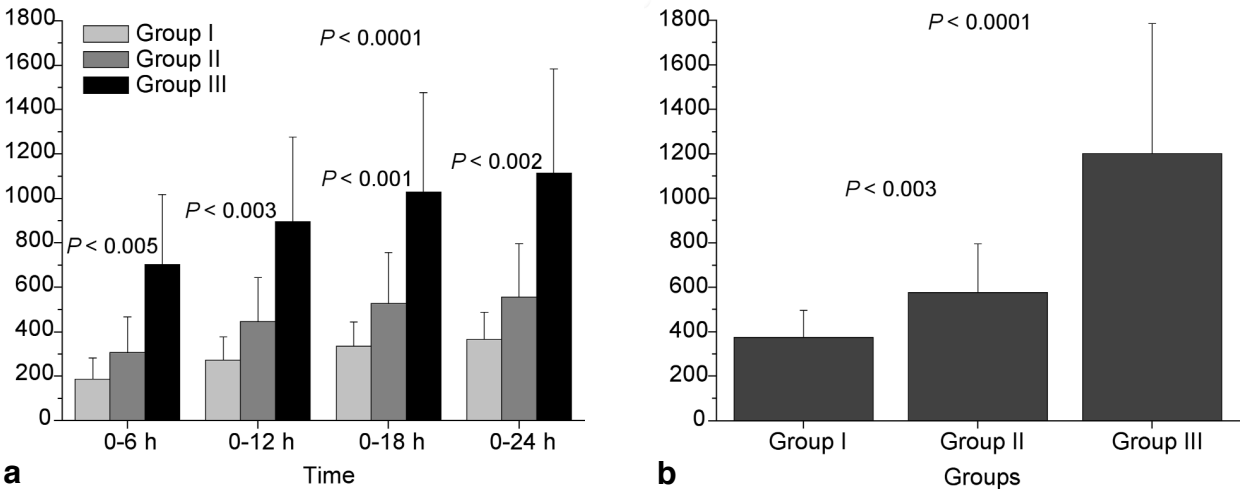

Fig. 1. Cumulative postoperative blood drainage within the first 24 h (a) and total blood loss before removal of the drains (b). Group I patients received a weight-related systemic high-dose aprotinin regimen and topical aprotinin applied in a dosage of 1.0 x 10^6 KIU into the pericardial cavity and onto the thoracic wound surface after resuming CPB during chest closure. Group II patients received a weight-related systemic high-dose aprotinin regimen only. Group III patients received neither systemic nor topical aprotinin during surgery. Data are expressed as mean (columns) and standard deviation (error bars).

Furthermore, Mannucci et al. detected elevated haemostatic variables in the systemic circulation as late as 1 month postoperatively [15]. Different low-dose intravenous aprotinin regimens have been shown to be less effective in reducing blood drainage than the high-dose Hammersmith regimen, which uses a fixed total dose of 6.0 10^6 KIU [22, 23, 25]. In our patients, a weight-based modification of the Hammersmith protocol was used, and it resulted in almost the same amounts of aprotinin as the standard Hammersmith protocol. The rationale for using topical aprotinin and its dose are based on the research of O'Regan and Tatar and the dose-volume considerations that led to the intravenous Hammersmith protocol [9, 33, 34]. It has been previously shown that topically applied aprotinin cannot be detected in the systemic circulation

Table 3. Perioperative transfusion requirements. Group I patients received a weight-related systemic high-dose aprotinin regimen and topical aprotinin applied in a dosage of 1.0 x 10^6 KIU into the pericardial cavity and onto the thoracic wound surface after resuming CPB during chest closure. Group II patients received a weight-related systemic high-dose aprotinin regimen only. Group III patients received neither systemic nor topical aprotinin during surgery.

	Groups									P value
	Intraoperative			Postoperative			Units / patient (total)			
	I	II	III	I	II	III	I	II	III	
A: Packed red blood cells							0.6	0.6	2.3	< 0.001
Number of patients	6 (27)	21 (85)	26 (60)	3 (27)	9 (85)	26 (60)				
Number of transfused units	10	31	64	6	17	75				
B: Packed thrombocytes							0.0	0.0	0.3	< 0.001
Number of patients	0	0	0	0	0	3 (60)				
Number of transfused units	0	0	0	0	0	17				
C: Fresh frozen plasma							0.0	0.0	1.2	< 0.001
Number of patients	0	0	0	0	0	22 (60)				
Number of transfused units	0	0	0	0	0	72				

Data are expressed as total values, n refers to the number of patients being transfused, in brackets total number of patients

and, therefore, does not lead to the development of the increased risks associated with higher aprotinin dosage, such as graft occlusion, thrombosis, and embolism [35].

Non-pharmacological blood-saving strategies, such as intraoperative haemodilution, autologous blood transfusions, ECC-blood retransfusion after resuming CPB, and cell-saver systems have been used more frequently in recent years. However, the effect of the use of these non-pharmacological blood-saving strategies on the therapeutic benefits and necessity of aprotinin in routine CABG has not been investigated [26, 36]. Therefore, the literature does not clearly indicate which patients received which blood-saving strategies in addition to aprotinin to control haemostasis. However, the use of other modalities is relevant, due to the considerable expense and possible adverse effects related to aprotinin. Thus, this study was done to evaluate the use of aprotinin in association with non-pharmacological blood-saving strategies. The present paper addresses these issues through a retrospective analysis of the records of patients undergoing routine elective CABG. Elective cases were chosen because they represent a homogenous population, unlike emergency cases, who often may have different bleeding risks due to an acquired coagulation disorder, as well as an overall higher morbidity and mortality due to non-optimal preoperative preparation. The patient groups that were analysed were well matched with respect to the key demographic characteristics and operative features, which is important in a retrospective study to permit comparison of the groups. This is in contrast to recent trials that assessed the risk associated with aprotinin during cardiac surgery but had imbalances between the groups in important factors, such as differences in drug dosages, type of operations, and history of disease, that can influence the outcomes [26]. Thus, an accurate selection and matching of patients could be more important than indiscriminately aggregating patients to obtain a large sample size.

In the present study, patients receiving both topical and systemic aprotinin had significantly less postoperative blood drainage (by 35%) than patients receiving only systemic high-dose aprotinin intravenously. Moreover, the postoperative blood loss was much higher (50%-70%) in patients who received no intraoperative aprotinin therapy, even after considering non-pharmacological blood-saving strategies. In patients receiving intraoperative haemodilution and autologous blood transfusions a trend towards lower postoperative blood drainage was seen, but it did not reach statistical significance, most likely due to the small sample size.

In recent years, the risk of transfusion-related infectious disease has drawn surgeons' and anaesthesiologists' attention to blood-saving strategies in cardiac surgery. Generally used techniques include: blood-saving operation and preparation techniques; irrigation of the wound surface with warm water; appropriate neutralisation of heparin with protamine after resuming extracorporeal circulation; adjustment of coagulation by repeated activated clotting time (ACT) measurement while still in the operating room; and timely warming of the hypothermic patient with heating blankets after surgery. However, retransfusion of shed mediastinal blood has not been shown to improve control of postoperative haemostasis [37]. To the best of our knowledge, the present analysis is the first study of the therapeutic effectiveness of intraoperatively administered aprotinin that has taken all of these blood-saving procedures into account. However, our goal was not to investigate the value of every single blood-saving method, but to determine the impact of the dif-

ferent intraoperative aprotinin therapies on blood loss and transfusion requirements when considering the presence of non-pharmacological blood-saving strategies that were used where appropriate. In this context, it has to be mentioned that aprotinin is the only haemostatic agent currently approved by the US FDA for use during CABG [38]. In the present study, patients receiving aprotinin during surgery had significantly reduced intra- and postoperative transfusion requirements compared to patients who did not receive aprotinin. However, the addition of topical aprotinin did not reduce postoperative transfusion requirements. This may be due to the fact that the postoperative banked donor blood requirement was very low in patients who received systemic high-dose aprotinin. Therefore, the use of additional topical aprotinin should be reserved for patients at high risk of bleeding. Though allergic reactions to aprotinin have been described, especially after re-exposure, such allergic reactions have been rarely reported in the literature; our findings also suggest that allergic reactions are rare. Furthermore, we did not observe any severe complications associated with aprotinin. We did observe a moderate, reversible increase of the serum creatinine level. Thus, this kallikrein inhibitor appears to be safe when appropriate selection criteria are used. However, one should be aware that there is a potential for nephrotoxicity associated with aprotinin. No aprotinin-related early graft occlusion was seen in this study, which coincides with what has been reported in the literature [39].

In conclusion, the present study found that locally and systemically administered aprotinin is safe and effective in reducing intra- and postoperative blood drainage and transfusion requirements. Thus, aprotinin should not be avoided during elective CABG when various blood-saving strategies are routinely used.

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