The Prophylactic Effect of Aprotinin on Intraoperative Bleeding in Liver Transplantation: A Randomized Clinical Study

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Fibrinolysis has been recognized as an important cause of intraoperative bleeding during orthotopic liver transplantation (OLT). Several investigators have used prophylactic administration of aprotinin in patients to inhibit fibrinolysis and to decrease transfusion requirements, morbidity, and mortality. Nevertheless, the role of aprotinin in this situation is not yet clear. The goal of this study was to determine the effects of prophylactic administration of aprotinin on intraoperative bleeding and blood requirements, and on hemostatic changes during OLT. Eighty consecutive patients were included in a double-blind, prospective study and were randomized in two groups. In group A (n = 39), an initial dose of 2×10^6 kallikrein inactivator units (KIU) of aprotinin was administered in the induction of anesthesia followed by infusion of 5×10^5 KIU/h until the end of the procedure. The control group (n = 41) received an identical volume of saline solution. The majority of the operations were performed with vena cava preservation (piggy-back technique) without venovenous bypass. During the anhepatic phase, a significant increase in levels of tissue plasminogen activator, thrombin-antithrombin complexes (TAT) and D-dimers (DD) was noted in both groups. A significant increment of TAT was observed in group A during reperfusion. The remaining hemostatic parameters were similar in both groups. Intraoperative requirements of packed red cells, fresh-frozen plasma (FFP), platelets, and cryoprecipitate were similar in the two groups. Our results suggest that prophylactic administration of aprotinin is not useful in reducing bleeding and blood product requirements during OLT. (HEPATOLOGY 1997;26:1143-1148.)

Orthotopic liver transplantation (OLT) is now a well-established procedure in the treatment of end-stage liver diseases.[1] Massive bleeding has been recognized as one of the main causes of morbidity and mortality in OLT.[2,3] The etiology of intraoperative hemorrhage is multifactorial. On the one hand, preoperative plaquetopenia is very common in patients with end-stage liver disease; they also present an important deficit in coagulation and inhibitor factors as a result of poor synthesis and clearance of these substances.[4] On the other hand, dilutional coagulopathy[5] can be a problem frequently encountered during the entire surgical procedure,[6] and fibrinolysis usually appears at the end of the anhepatic phase and the beginning of the reperfusion of the graft.[7-9] Therefore, there is a growing interest in the possible benefits obtained in intraoperative bleeding with the use of prophylactic and therapeutic antifibrinolytic agents.[10,11]

Aprotinin is a polypeptide with antifibrinolytic effects that has been reported to decrease operative bleeding in open heart surgery.[12-15] The benefits of aprotinin's prophylactic administration have also been studied in OLT to reduce intraoperative bleeding.[16-30] However, the majority of papers published until now have been nonrandomized retrospective studies, or the number of patients included was too small for conclusions to be drawn.[16-30] Therefore, the exact role of aprotinin in OLT has yet to be clearly determined.

The purpose of this paper was to establish the value of prophylactic administration of aprotinin in OLT in a prospective randomized double-blind study.

PATIENTS AND METHODS

After institutional approval, written consent to enter in the study was given by all patients who underwent OLT between June 1991 and December 1993.

Exclusion criteria were retransplantation within less than 3 months, multiorgan transplantation, and acute liver failure. A total of 121 OLTs were carried out during the study period. Forty-one of these patients were excluded due to the unavailability of aprotinin (16 cases), intraoperative death (1 case), simultaneous kidney and liver transplantation (3 cases), and immediate retransplantation (4 cases). Seventeen patients were excluded because of a lack of data to fulfill the analysis.

Patients included in the study were stratified according to the preoperative value of plasmatic antithrombin III (superior or inferior to 0.7 IU/mL), and whether or not they had undergone previous surgery in the upper abdomen. Following stratification, patients were randomized in two groups, as follows: 1) the aprotinin group, 39 patients who received 2 million kallikrein-inactivator units (KIU) during the anesthesia induction, followed by infusion of 5×10^5 KIU/h until the end of the surgical procedure; and 2) the control group, 41 patients who received an identical volume of saline solution. All OLTs were performed by the same surgeons and anesthesiologists, and the medical team was blinded about patient allocation.

Anesthesia was performed with 0.2 mg/kg of midazolan, or 3 mg/kg sodium thiopental, 0.3 mg fentanyl, and 0.10 mg/kg pancuronium, and was maintained by continuous infusion of the same

Abbreviations: OLT, orthotopic liver transplantation; KIU, kallikrein-inactivator units; F_iO_2, inspired oxygen fraction; TAT, thrombin-antithrombin III complexes; DD, D-dimer; FFP, fresh-frozen plasma; AG, aprotinin group; F_iO_2, inspirated oxygen fraction; PT, prothrombin time; APTT, activated partial thromboplastin time; AT III, antithrombin III; α-AP, α2-antiplasmin; PC, protein C; PDFna, fibrin degradation products; t-PA, tissue plasminogen activator; PAI-1, plasminogen activator inhibitor; u-PA, urokinase plasminogen activator.

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drugs. Mechanical ventilation was begun at 12 mL/kg with a respiratory rate in order to obtain partial pressure of 35 mm hg CO_2 and an inspired oxygen fraction (F_iO_2) of 0.5 in air, except before the unclamping of the graft when it was raised to a F_iO_2 of 1%. Calcium was administered to maintain plasma ionic calcium levels between 1 and 1.2 mmol/L and sodium bicarbonate 1/6 molar to reach a pH of greater than 7.30. Saline solution was perfused at a rate of 15 mL/kg/h. All patients were placed on a warm blanket (Warmtouch, Mallinkrodt, Athlone, Ireland), lower limbs were isolated with cotton and aluminum foil, warm serums were administered by means of a rapid infusion system, and room temperature was maintained between 26° to 28°C.

Most of the surgical procedures were performed with vena cava preservation (piggy-back technique). A femoral-portal-axillary venovenous bypass was used in patients with limited cardiac reserve and pulmonary hypertension.

Prior to reperfusion of the graft, the liver was flushed with portal blood, discarding the first 300 to 400 mL.

Criteria for Blood Product Administration. To compensate for blood loss, packed red blood cells were administered to maintain hematocrit levels at 30% and hemoglobin at 100 g/L. Fresh frozen plasma (FFP) was given to obtain dependent vitamin K coagulation factors and factor V over 0.5 UI/mL, and the prothrombin time ratio below 1.5.

Platelets were administered to maintain values over 50×10^9/L and cryoprecipitate was added to reach fibrinogen levels higher than 2 g/L.

Biological Tests. Blood samples were taken during induction, dissection, and the anhepatic phase, at 5 minutes and 1 hour after reperfusion of the graft and at the end of the surgical procedure. Samples were collected on sodium citrate 0.129 in the proportion of 1/9 and immediately centrifuged at 2,000*g* for 10 minutes. The biological tests performed included: Prothrombin Time (PT) (PT-Fibrogen HS, IL, Milan, Italy); Activated Partial Thromboplastin Time (APTT) (APTT Lyophilized Silica, IL, Milan, Italy); Fibrinogen using Clauss' functional method (Fibrinomat, BioMerieux, Marcy l'Etoile, France); Thrombin Time, using human thrombin (Fibrindex, Ortho Diagnostics Systems, Raritan, NJ); Reptilase Time (Fibroclotin, Grifols, Parets del Vallés, Barcelona, Spain); Factors II, V, VII, and X, using the coagulation method on plasma without Factors II, V, VII, and X (Hepatocomplex, IL, Milan, Italy); the activity of AT III (Coamate antithrombin), α2-antiplasmin (α2-AP) (Coatest antiplasmin); plasminogen (Coatest plasminogen) and protein C (PC) (Coamate protein C) were determined by amiolytic methods (Chromogenix, Mondal, Sweden). Coagulation and amiolytic tests (with the exception of fibrinogen determination performed on KC-10, Amelung, Germany) were carried out on ACL 300R (IL, Milan, Italy). Tissue plasminogen activator (t-PA) (Tint-Elize t-PA), as well as Plasminogen Activator Inhibitor (PAI-1) were determined by ELISA (Biopool, Umea, Sweden), as were D-dimer (DD) (Fibrinostika FbDP, Organon Teknika, Boxtel NL) and Thrombin-Antithrombin Complexes (TAT) (Enzygnost TAT, Behring, Malburg, Germany).

It should be emphasized that the presence of aprotinin in plasma led to interference in the α2-AP determinations (increased activity), plasminogen and protein C (reduced activity), and activated partial thromboplastin time (prolonged time).

Other variables recorded were cold and warm ischemia time, the duration of the anhepatic phase, blood product requirements, the need for reoperation due to intraabdominal bleeding, postoperative vascular thrombotic complications, and mortality.

Statistical Analysis. An α-error of 0.05 and a 30% decrease in transfusion requirements was considered clinically significant.

All data are presented as mean and standard deviation (mean ± SD). Matched-pairs Student's *t* test was used for comparison of continuous variables between both groups. The χ^2 test was used for discontinuous variables. Differences were considered significant at a $P < .05$ level.

TABLE 1. Demographic and Preoperative Status

	Aprotinin Group (n = 39)	Control Group (n = 41)
Age (yr)	50 (15-64)	50 (17-65)
Sex (no. male)	24 (62%)	27 (66%)
Previous surgery (n)	12 (31%)	12 (29%)
Diagnosis (n)		
Liver cirrhosis	28 (72%)	17 (41%)
Hepatocellular carcinoma	8 (21%)	11 (27%)
Primary biliary cirrhosis	2 (5%)	4 (10%)
Retransplantation	1 (2%)	5 (12%)
Miscellaneous*	0	4 (10%)
Preoperative Laboratory Values (mean ± SD)		
Prothrombin times (ratio)	1.5 ± 0.3	1.4 ± 0.4
Platelet count (10^9/L)	102 ± 87	113 ± 82
Fibrinogen (g/L)	2.7 ± 1.7	2.9 ± 1.5
Antithrombin III (IU/mL)	0.54 ± 0.23	0.59 ± 0.26

Abbreviations: AG, aprotonin group; CG, control group.

* Miscellaneous: sclerosing cholangitis (n = 1), intrahepatic biliary hypoplasia (n = 1), Budd-Chiari syndrome (n = 1), autoimmune hepatitis (n = 1).

TABLE 2. Surgical Procedure

	Aprotonin Group (n = 39)	Control Group (n = 41)
Cold ischemia time (min)	520 ± 223	463 ± 176
Warm ischemia time (min)	52 ± 12	44 ± 12
Anhepatic phase (min)	69 ± 25	68 ± 21
Piggy-back technique (n)	28 (72%)	33 (80%)
Venous cava clamp (n)	11 (28%)	8 (20%)
Venovenous bypass (n)	4 (10%)	2 (5%)

RESULTS

Demographic data are shown in Table 1. Both groups were similar regarding age, sex, and previous upper abdominal surgery. All patients with hepatocellular carcinoma also had a concomitant cirrhosis, as did patients with autoimmune hepatitis. The total number of patients with cirrhosis was 38 in group A and 33 in group C. Therefore, although it would seem that there was a greater number of patients with diagnosis of liver cirrhosis in the aprotinin group, there were no differences in the preoperative values of hemostasis.

No differences were observed between the two groups in cold and warm ischemia time, the duration of the anhepatic phase, or in the use of venovenous bypass (Table 2).

During the anhepatic phase, there was a moderate but significant decrease in the number of platelets, and a highly significant increase in t-PA, TAT complexes and DDs in both groups.

At the beginning of the reperfusion phase t-PA values decreased slightly, although there was no significant difference in relation to basal values. Levels of PAI-1 increased in both groups and levels of TAT complex were significantly higher in patients who received aprotinin (Fig. 1). DD levels were similar in both groups (Table 3).

One hour after reperfusion the concentration of TAT complexes tended to be higher in the aprotinin group, although this was not significant. The levels of DD and PAI-1 remained high in both groups, whereas t-PA levels decreased (Table 3).

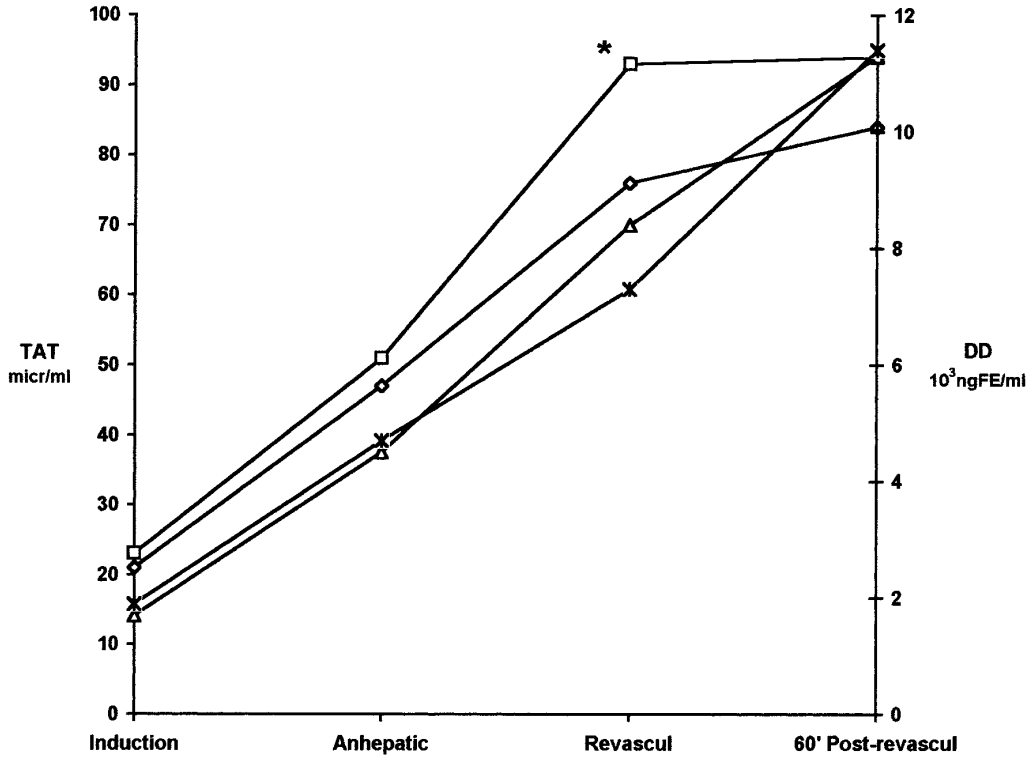

FIG. 1. Mean changes in TAT and DD titers. *Statistically significant difference between aprotinin group (AG) and control group (CG)($P < .05$). (◇) TAT (CG); (□) TAT (AG); (△) DD (CG); and (★) DD (AG).

No statistically significant difference was observed between groups regarding blood product requirements during OLT (Table 4). Twenty-four hours after orthotopic liver transplantation, 20 patients in the control group (49%) and 13 in the aprotinin group (34%) required transfusion of red blood cells (RBC) without statistical differences (Table 4).

The high doses of aprotinin were well tolerated by all patients and no allergic reactions were observed.

One patient from the aprotinin group required retransplantation on the third day due to thrombosis of both the hepatic artery and the portal vein. The problem was attributed to technical difficulties encountered during surgery in a patient with a previous major hepatic resection. Two patients in the control group required urgent retransplantation, on the second and fifteenth day, due to primary nonfunctioning graft.

Reoperation due to intraabdominal hemorrhage was necessary in five patients during the late postoperative period and no differences were observed between the two groups. Reoperation due to hemorrhage was carried out in two patients in the aprotinin group on days 11 and 34, and in three patients in the control group, one on day 14 and another on day 20, due to spontaneous rupture of the splenic vein leading to intraoperative death, and the third on day 15 due to diffuse gastric hemorrhage, also with a fatal outcome.

One aprotinin group patient died on day 12 after transplantation due to multiorgan failure and one control group patient died on day 27 due to cardiorespiratory failure.

DISCUSSION

Intraoperative bleeding can be an important concern during OLT, and this may be due to various factors such as hemostatic changes, the surgical technique, and preexisting local conditions, which include portal hypertension, previous abdominal surgery, and ascites. Massive transfusion is sometimes necessary, and it has been recognized as the main cause of the morbidity and mortality of the procedure.[31]

The hemostatic condition of the patient undergoing OLT is usually deteriorated due to the advanced hepatic disease. The hemostatic changes most frequently encountered[32] are a deficit in the hepatic-dependent coagulation factors and in the coagulation inhibitors, and an increase in fibrinolytic activity.[33] Thrombocytopenia is also a frequent finding and is secondary to hypersplenism and to a decrease in platelet aggregability.

Hepatectomy is characterized by extensive surgical dissection and portal hypertension. Previous operations and the expertise of the surgical team are determining factors of bleeding during this period. In our study, the majority of the operations were performed with vena cava preservation (piggy-back technique) without venovenous bypass. There is only a randomized trial that compares vena cava preservation and the classical technique with venovenous by-pass[34]; in this study, no statistically significant differences were found with regard to intraoperative hemodynamics, blood loss, and transfusion with the classical technique. Therefore, we believe the results of our study may be applicable to all OLT performed with different techniques.

During the anhepatic phase, numerous studies have detected an increase of fibrinolysis with a decrease of α2-AP and plasminogen,[8,9] elevated t-PA,[7,35] and a decrease in the FV/FII and FV/FVIII quotients. It has been suggested that t-PA plays an important role in the origin of bleeding, and high levels of t-PA have been associated with increased transfusion requirements.[7,35]

A heparin-like effect may appear during reperfusion due to the elimination of heparin or heparin-like factors of the graft with an increase of TTPA. This can be treated with

TABLE 3. Perioperative Coagulation Parameters

	Normal Values	Group	Induction	Anhepatic Phase	5′ Post-Reperfusion	60′ Post-Reperfusion
PT (ratio)	<1.2	CG	1.46 ± 0.41	1.29 ± 0.25	1.42 ± 0.28	1.41 ± 0.25
		AG	1.63 ± 0.46	1.28 ± 0.27	1.38 ± 0.26	1.77 ± 1.81
FV (IU/mL)	≥0.7	CG	0.58 ± 0.26	0.65 ± 0.16	0.56 ± 0.17	0.50 ± 0.17
		AG	0.50 ± 0.25	0.65 ± 0.19	0.52 ± 0.13	0.44 ± 0.14
FVKD (IU/mL)	≥0.8	CG	0.55 ± 0.25	0.67 ± 0.20	0.57 ± 0.18	0.59 ± 0.15
		AG	0.45 ± 0.18	0.63 ± 0.19	0.53 ± 0.12	0.50 ± 0.12
Fibrinogen (g/L)	2.0-4.0	CG	2.52 ± 1.17	2.69 ± 0.93	2.41 ± 0.78	2.46 ± 0.72
		AG	2.40 ± 1.41	2.82 ± 1.27	2.48 ± 0.82	2.58 ± 0.79
AT III (IU/mL)	0.8-1.2	CG	0.61 ± 0.31	0.71 ± 0.23	0.64 ± 0.22	0.95 ± 1.58
		AG	0.52 ± 0.27	0.74 ± 0.22	0.71 ± 0.18	1.02 ± 1.61
PC (IU/mL)	0.7-1.4	CG	0.52 ± 0.28	0.72 ± 0.20	0.67 ± 0.19	0.67 ± 0.18
		AG	0.44 ± 0.31	0.59 ± 0.17	0.56 ± 0.16	0.55 ± 0.15
TAT (μg/mL)	1.0-4.1	CG	20.99 ± 23.59	47.05 ± 30.20	76.28 ± 30.37	83.66 ± 33.43
		AG	23.25 ± 25.39	51.18 ± 30.87	92.82 ± 35.15*	94.27 ± 35.56
t-PA (ng/mL)	1.0-20.0	CG	21.95 ± 17.03	33.47 ± 18.81	28.65 ± 17.94	23.71 ± 14.68
		AG	23.27 ± 16.54	31.26 ± 19.62	31.16 ± 19.29	23.58 ± 18.86
PAI-1 (ng/mL)	18 ± 10	CG	32.06 ± 16.59	33.96 ± 14.76	39.22 ± 12.63	47.28 ± 18.08
		AG	27.59 ± 13.85	35.32 ± 14.48	36.43 ± 12.41	54.40 ± 54.04
t-PA/PAI-1		CG	0.86 ± 0.74	1.16 ± 0.85	0.89 ± 1.20	0.56 ± 0.45
		AG	1.14 ± 1.64	0.92 ± 0.52	0.91 ± 0.56	0.60 ± 0.74
Plasminogen (IU/mL)	0.6-1.4	CG	0.61 ± 0.27	0.74 ± 0.19	0.68 ± 0.24	0.75 ± 0.22
		AG	0.48 ± 0.24	0.53 ± 0.17	0.55 ± 0.17	0.52 ± 0.15
α2-AP (IU/mL)	0.8-1.2	CG	0.73 ± 0.20	0.81 ± 0.17	0.73 ± 0.16	0.75 ± 0.21
		AG	0.96 ± 0.36	1.05 ± 0.15	1.00 ± 0.16	1.02 ± 0.16
DD (ng FE/mL)	<310	CG	1,742 ± 1,701	4,533 ± 7,314	8,403 ± 9,586	11,325 ± 20,111
		AG	1,961 ± 1,921	4,775 ± 5,121	7,312 ± 8,286	11,434 ± 13,456
Platelets ($\times 10^9$/L)	130-400	CG	107 ± 91	82 ± 61	78 ± 50	79 ± 52
		AG	100 ± 99	69 ± 54	74 ± 45	69 ± 44
Hemoglobin (g/L)	120-180	CG	100 ± 20	100 ± 20	98 ± 18	93 ± 21
		AG	104 ± 20	106 ± 20	100 ± 20	94 ± 17

NOTE. Data given as mean ± SD.

Abbreviations: PT, prothrombin time; FV, factor V; AT III, antithrombin III; PC, protein C; TAT, thrombin-antithrombin III complexes; t-PA, tissue plasminogen activator; PAI-1, plasminogen activation inhibition; α2-AP, α-2-antiplasmin; DD, D-dimer; CG, control group; AG, aprotinin group.

* $P < .05$.

infusion of protamine sulphate.[36] However, other causes of bleeding can also be encountered during reperfusion, such as thrombocytopenia due to platelets atrappement in the graft and poor platelet function.[9] Consumption coagulopathy is characterized by a high increase of TAT and Fibrin Degradation Products (PDFna),[37] and a decrease in AT III and total and free Protein S.[38] It has been suggested that the coagulation changes detected after reperfusion are induced by the release of mediators from the grafted liver, and depends, to a great extent, on the correct preservation of the graft.[39-41]

Hyperfibrinolysis[20] is associated with a marked increase of t-PA, and a decrease in the lysis time of euglobulines and clot lysis time. Furthermore, a decrease in the levels of inhibitors (α_2-antiplasmin, α_1-antitripsin, and α_2-macroglobulin) due to consumption is also present.[42] High levels of t-PA and antigenic urokinase plasminogen activator (u-PA) have also been detected in the effluent of the graft washout.[43] Nevertheless, the fibrinolytic activity usually returns to normal values within the first two hours, associated with the functional recuperation of the grafted liver.[9]

TABLE 4. Blood Product Requirements During OLT and 24 Hours Posttransplantation

	Group	Dissection	Anhepatic Phase	60 min Postreperfusion	Total	24 h Post-transplantation
RBC (U)	AG	5.7 ± 4.4	2.5 ± 2.0	2.0 ± 1.7	13.0 ± 8.0	2.4 ± 1.4
	CG	5.6 ± 4.8	2.6 ± 2.4	2.6 ± 2.3	14.4 ± 9.7	2.4 ± 0.9
FFP (U)	AG	13.8 ± 8.8	4.9 ± 4.0	3.8 ± 3.4	26.0 ± 16.0	3.5 ± 2.5
	CG	14.4 ± 10.7	5.0 ± 5.9	4.6 ± 3.1	28.0 ± 15.0	3.8 ± 2.1
Platelets (patients)	AG	6 (15%)	—	29 (74%)	29 (74%)	12 (31%)
	CG	4 (10%)	—	25 (70%)	25 (70%)	15 (37%)
Cryoprec (patients)	AG	5 (13%)	—	21 (54%)	21 (54%)	—
	CG	3 (7%)	—	22 (54%)	22 (54%)	—

NOTE. Data given as mean ± SD.

Abbreviations: RBC, red blood cells; Crioprec, cryoprecipitates; AG, aprotinin group; CG, control group.

Fibrinolysis has been considered an important factor in the genesis of bleeding, therefore, different groups have suggested the possibility of using aprotinin prophylactically during OLT.[16-30] Aprotinin is a nonspecific inhibitor polypeptide of the serinproteases that acts through the lysine residue on the serine of these proteins, and forms reversible stoichiometric complexes. Aprotinin is able to inhibit the plasmin and kallikrein,[14] protein C (mainly in the presence of heparin),[44] and, to a lesser degree, u-PA, elastase, thrombin and other proteins. Aprotinin has a half-life in blood of 37 minutes, and it is mainly eliminated through the kidney. Nevertheless, the mechanism underlying the beneficial effects of aprotinin have not yet been completely described. There are studies that suggest that aprotinin reduces the production of t-PA during OLT, probably by inhibiting the kallikrein and bradykinin, a potent stimulator of the t-PA release.[19,21,27,30] It probably also has a direct platelet preserving property.[7] However, in our study, the decrease in t-PA from aprotinin was not confirmed, because the levels of t-PA in the aprotinin group were the same as in the control group.

Segal et al.,[45] in a nonrandomized study, administered 2×10^6 KIU of aprotinin at the start of surgery with a maintenance dose of 0.5×10^6 KIU/h, a bolus of 1×10^6 KIU when starting venovenous bypass, and 50,000 KIU to each unit of product red blood cells and the blood levels obtained were 200 KIU/mL during the anhepatic phase. Others used continuous perfusion of smaller quantities ($0.1\text{-}0.4 \times 10^6$ KIU/h)and obtained blood levels of 50 to 110 KIU/mL.[22,41,46] In our study, we used a higher dose than in previous reports (an initial dose of 2×10^6 KIU of aprotinin in the induction of anesthesia followed by infusion of 5×10^5 KIU/h until the end of the procedure) because no deleterious effects have been described, and to ensure suitable blood levels.

Several studies, using different doses and methodology, all based on the comparison with a historical control group, observed a decrease in the blood product requirements.[19,26-28] However, the results are difficult to compare because there is a broad range of doses of aprotinin, and the methodology of administration (bolus or continuous perfusion) is also different. Betchstein et al.[26] studied 46 OLT with administration of three boluses of 5×10^6 KIU during the induction, the anhepatic phase, and during reperfusion, and compared them with those of a historical group. They did not find any difference in the transfusion of P.R.B.C. units (aprotinin 7.5 ± 4.6 vs. control 9.7 ± 5.5).

Groh et al.,[23] in a randomized placebo-control trial, studying 10 versus 10 patients with administration of 2×10^6 KIU of aprotinin at the induction of anesthesia and continuous infusion of 5×10^5 KIU/h, did not observe any difference regarding the intraoperative needs of packed red blood cells, FFP, or platelet transfusion, but the number of patients was too small to draw conclusions.

Our study is unique because it is the first randomized prospective study investigating whether prophylactic administration of aprotinin has an impact on hemostasia and blood transfusion. The number of cases is large enough to draw conclusions, and demonstrates that there is no advantage in giving aprotinin in liver transplantation.

It has been suggested that aprotinin may benefit the patients who bleed most, but this hypothesis was not confirmed in our study. We analyzed the patients with blood requirements superior to 20, 20 to 10, and less than 10 packed red cells units, and the patients of the aprotinin group and control group were distributed uniformly between the three groups. Postoperative blood transfusion was also similar in both treatment groups (Table 4).

In our study, α_2-AP levels in the control group remained stable throughout the surgical procedure, whereas a decrease would be expected due to the fast plasmin-α_2-AP reaction related to systemic fibrinolysis. The high levels of α_2-AP detected in the aprotinin group are caused by the interference with the assay system due to the aprotinin by itself (42 KIU of aprotinin is equivalent to 1 IU of antiplasmin when used alone in the assay).[45]

A significant increase of t-PA during the anhepatic phase, and a decrease during reperfusion, were observed in both groups. The decrease of t-PA observed during reperfusion may be due to the clearances function of the new liver graft and to the linking of the t-PA with the PAI-1, which increases after reperfusion. In view of these results, it may be hypothesized that t-PA may not play as an important a role in the genesis of fibrinolysis during OLT as it has been reported, and consequently, the utility of aprotinin may also be questioned.[46]

It could be expected that the prophylactic administration of aprotinin would lead to a decrease in local fibrinolysis. However, in such a case, we would observe a lower concentration of DD in the treated group, as has been observed in cardiac surgery.[47,48] We did observe an increase in the formation of systemic thrombin during reperfusion induced by aprotinin and associated with an increase in the TAT of the aprotinin group (Table 3, Fig. 1).

Himmelreich et al.[43] detected higher levels of TAT in the group receiving continuous perfusion with respect to the group of 3 boluses of 5×10^5 KIU, and it has been hypothesized that this increase is probably secondary to the inhibition of active C protein.[44] In our study, we also found low levels of C protein in the aprotinin group during the entire procedure. However, this increase in the formation of thrombin, which does not imply an increase in fibrin formation, does not appear to be related to a better or worse prognosis.

No complications related to aprotinin administration were observed in our study. The only case of thrombosis of the hepatic artery and vena porta in the aprotinin group was attributed to difficulties encountered in the surgical technique.

In summary, the causes of operative bleeding in OLT are multifactorial. Transfusion requirements are clearly affected by the expertise of the surgical team, the monitorization, and awareness of the hemostatic alterations. Ischemic injury of the graft may influence primary fibrinolysis following reperfusion. In our study, we did not find any difference in the blood product requirements in patients who received intraoperative prophylactic treatment with aprotinin at doses of 2×10^6 KIU in boluses followed by perfusion of 5×10^5 KIU/h, in comparison with the control group. Prophylactic administration of aprotinin does not, therefore, appear to offer any beneficial effect on bleeding during OLT. Further studies are necessary to evaluate the efficacy of this drug in a subgroup of patients at high risk of intraoperative bleeding.

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