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Hemostasis and blood requirements in orthotopic liver transplantation with and without high-dose aprotinin

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Abstract

Background and Objective. **Several factors seem to lead to considerable bleeding and transfusion requirements during orthotopic liver transplantation (OLT) and postoperatively, but hyperfibrinolysis appears to be the most important factor. Aprotinin, a broad-spectrum serine protease inhibitor, has been shown to inhibit hyperfibrinolytic states.**

Design and Methods. **A non-randomized, controlled clinical trial was performed to assess the efficacy of aprotinin in 20 consecutive OLT procedures (group A). The results obtained were compared with the findings in two groups of patients who did not receive aprotinin: one control group (C1) consisting of the 20 consecutive recipients who underwent OLT immediately prior to group A, and a second control group (C2) consisting of the 30 consecutive recipients undergoing OLT immediately after group A. Twenty-three hemostatic parameters were studied in group A and C1 and the blood product requirements were compared in all three group.**

Results. **We observed a markedly reduced fibrinolysis in group A during the non-hepatic and reperfusion phases demonstrated by reduced tissue-type plasminogen activator (t-PA), α_2 antiplasmin-plasmin complex (APP) and D dimer levels and an increase in antiplasmin activity compared to C1 group ($p < 0.05$). *In vitro* experiments showed aprotinin to have an antiplasmin effect. The intraoperative transfusion of units of RBC and fresh frozen plasma (FFP) was significantly diminished in group A (8.1 and 16.7 U, respectively) when compared with groups C1 (20.4 and 36.0 U) and C2 (13.0 and 28.0 U) ($p < 0.05$); there was also a significantly greater number of patients not requiring intraoperative platelet transfusion in group A ($p < 0.05$). During the first 5 postoperative days, the number of patients in group A who did not require RBC transfusion was significantly larger than in groups C1 and C2 ($p=0.04$).**

Interpretation and Conclusions. **In this study, the inhibition of fibrinolysis associated with the prophylaxis with aprotinin, administered in high doses by continuous intravenous infusion, appears to reduce the need for blood product transfusion during the OLT procedure.**

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Orthotopic liver transplantation (OLT) has become the treatment of choice for a large number of patients with end-stage liver disease.[1] Nevertheless, despite the improvements that have taken place in graft preservation, surgical and anesthetic techniques, and the perioperative management,[2] OLT can be associated with severe bleeding and considerable transfusion requirements, which in turn greatly contribute to the perioperative morbidity and mortality.[3]

Several factors seem to lead to excessive bleeding during OLT, but hemostatic abnormalities remain a major cause.[4,5] The hemostatic disorder is multifactorial and is related to a preexisting coagulopathy due to the underlying liver disease and to the procedure of liver transplantation itself; hyperfibrinolysis appears to be the most important factor, chiefly occurring late in the anhepatic phase and immediately after the reperfusion of the graft.[6] This enhanced fibrinolytic activation is due to an excess of tissue-type plasminogen activator activity (t-PA) on account of the lack of hepatic clearance and its increased release from the ischemically-damaged endothelium, associated with a consumption of α_2-antiplasmin and plasminogen activator inhibitor type 1 (PAI 1).[7-9]

Prophylactic antifibrinolytic treatment has not been regularly employed in OLT. There are two antifibrinolytic agents that have been successfully used by some groups: epsilon-aminocaproic acid (EACA) and aprotinin.[10,11] The broad-spectrum serine protease inhibitor, aprotinin (Trasylol®),[12] has been shown to reduce both intraoperative and postoperative bleeding and transfusion requirements in a variety of surgical procedures, including open heart surgery,[13] and it has recently been used during OLT to prevent excessive blood loss.[14] Aprotinin inhibits plasmin and kallikrein at a concentration that clinically can be reached. Besides, it has also been suggested that aprotinin may preserve platelet function.[15]

The aim of this study was to investigate the effects of aprotinin on the coagulation and fibrinolytic systems on blood requirements of patients undergoing OLT.

Patients and Methods

Patients

We recruited seventy consecutive adult patients undergoing OLT for end-stage liver disease between May 1991 and July 1994. They were included in a non-randomized controlled clinical trial, designed to assess the clinical relevance of hyperfibrinolysis during OLT and to evaluate the role of aprotinin on surgically-induced fibrinolysis activation. Written informed consent was obtained, and patients were put into groups according to date of surgery as follows: *control 1* (C1) group, 20 patients May 1991-October 1992); *aprotinin-treated group* (A), 20 patients (October 1992-July 1993); and *control 2* (C2) group, 30 patients (July 1993-July 1994). All three groups were comparable regarding surgical and anesthetic techniques used. No veno-venous bypass was carried out in any patient.

Aprotinin regimen

Group A received a loading dose of 2×10^6 kallikrein-inhibitory units (KIU) after the induction of anesthesia, followed by a continuous intravenous infusion of 0.5×10^6 KIU/h until skin closure (Trasylol®; Bayer AG, Leverkusen, Germany). An additional dose of 50,000 KIU was given per unit of packed red blood cells (RBC) transfused.

Clinical evaluation

The following clinical variables were evaluated in each patient: aprotinin-induced side effects, perioperative occurrence of infectious and surgical complications (thrombotic, hemorrhagic and others) developed in the early postoperative period (within 3 months of post-transplantation); length of surgery; time to extubation; serum creatinine levels (mg/dL) preoperatively and in the first month of post-transplantation, and mortality in the first month post-transplantation. The number of units of RBC, fresh frozen plasma (FFP) and platelet concentrates (PC) transfused during the surgical procedure and daily for the first 5 days post-transplantion were also analyzed.

Blood product transfusion policy. RBC were transfused to maintain hematocrit >30%. FFP was given in a 1:1 or 1:1.5 proportion with respect to RBC volume and according to the degree of coagulopathy (to keep prothrombin time > 50% normal; i.e. < 20 sec). PC were given to keep platelets above 50×10^9/L. Blood components warmed to 37°C were infused. A rapid blood infusion was employed (Hemocare PLB 36, Brevets G, Le Boeuf, France) when required. No cell-saver machine was used.

Sample collection

Eleven blood samples were obtained from each patient of groups C1 and A during the several phases of surgery as follows: a) preoperatively; b) in the preanhepatic phase (5 minutes before the beginning of the anhepatic phase); c) 10 minutes into the anhepatic phase; d) at the end of the anhepatic phase (5 minutes before the beginning of revascularization); e) 10 minutes after the reperfusion of the graft; f) 70 minutes after graft reperfusion; and daily for the first 5 days post-surgery (+1, +2, +3, +4, +5).

Assay methods

Twenty-three coagulation and fibrinolysis parameters were determined in each blood sample. Prothrombin activity (PA), aPTT, thrombin time (TT), fibrinogen (FG) level, platelet count, and hemoglobin level were immediately analyzed after blood sampling. The remaining parameters were determined later on in the aliquots of plasma that had been immediately frozen and stored at –70 °C.

Hemoglobin and platelet count were assessed using a Coulter Counter S Plus PA, aPTT, TT and FG were done manually or using an MLA Electra 900. Quantification of factors II, V, VII, X, VIII:C, IX, XI and XII was made automatically on a MLA Electra 900 coagulometer (all reagents were supplied by Baxter-Dade, Miami, FL, USA).

Functional activities of antithrombin III (AT III), protein C (PC), plasminogen (PG) and α_2-antiplasmin (AP) were measured using chromogenic substrate assays (Baxter-Dade). Enzyme-linked immunoabsorbent assays were used to determine the thrombin-antithrombin complex (TAT) (Enzygnost-TAT, Behringwerke, Marburg, Germany), tissue-type plasminogen activator (t-PA) antigen (Coaliza t-PA, Kabi, Stockholm, Sweden), α_2 antiplasmin-plasmin complex (APP) (EIA APP micro, Behring, Marburg, Germany), plasminogen activator inhibitor type 1 (PAI 1) (Asserachrom PAI-1, Diagnostica Stago, Asnières, France) and D-dimer (Dimertest EIA kit, American Diagnostica).

Normal reference values were as follows: coagulation factors II, V, VII, X, VIII:C, IX, XI and XII: 50-150%, AT III activity: 80-120%, PG: 80-120%, AP: 80-120%, PC: 70-130%, TAT: 1.0-4.0 ng/mL, t-PA: 1-12 ng/mL, PAI 1: 4-43 ng/mL, D dimer: 0-25 ng/dL, APP: 80-470 mg/L.

Statistical analysis

The chi-square test (p values corrected with Yates' method) was used to compare qualitative variables; the Student t-test was employed to examine differences among quantitative data. The BMDP Statistical Software package (UCLA) was used for testing data. Quantitative data are presented as the mean ± standard deviation (SD). Significant differences among groups were studied using a one-way analysis of variance (ANOVA) for independent samples together with a multiple comparison among groups (Newman-Keuls). For differences among samples within patient groups (repeated measurements), ANOVA for correlating samples and the non-parametric Mann-Whit-

Table 1. Clinical characteristics of the patients.

	Group C1 n=20	*Group A n=20*	*Group C2 n=30*
Age (years)	49±14 (20-66)	46±12 (16-61)	46±7 (16-62)
Sex (M/F)	12/8	13/7	20/10
Diagnosis			
liver cirrhosis	18	17	23
cholestasis disease	0	1	2
acute hepatic failure	1	1	2
liver malignancy	1	1	3
Child-Pugh score			
A	5	2	2
B	11	10	19
C	4	8	9
Cold ischemia time (hours)	6.9±2.7 (4-13)	6±2 (3-9.5)	6±2 (3-10)

Were applicable, data were expressed as mean ± SD (range). No statistically significant differences were seen among groups.

ney test were performed. P values < 0.05 were taken as statistically significant. A Pearson correlation was calculated to show the relationship between transfusion rates and length of the surgical procedure.

Results

All three groups were comparable, with no differences among them regarding to age, sex, diagnosis of liver disease, severity of liver disease according to the Child-Pugh score, cold ischemia time, use of veno-venous bypass or preoperative hemostatic variables. The most common underlying liver disease was cirrhosis. Patient data are shown in Table 1. Because of this similarity among groups, we decided to perform the analysis of the hemostatic parameters only in groups C1 and A.

Results of the coagulation assays

The preoperative coagulation parameters studied showed abnormalities in groups C1 and A, with no significant differences between them (Table 2).
Hemoglobin, platelet count (Figure 1), PA and extrinsic pathway coagulation factors (factors VII, X, V, II) were not significantly different between the two groups throughout the intraoperative and postoperative periods. During surgery, fibrinogen showed a slight decrease in both groups until the reperfusion phase was reached, afterwards falling and resulting in a lower level in group C1 than in group A (200±62 mg/dL vs 236±72 mg/dL) (p=0.09). In both groups, pathway coagulation factors were indeed lower than normal during the surgical procedure, but factors XII, XI, IX, VIII:C were lower in group A during the reperfusion of the graft compared to group C1 (p < 0.05) (Figure 2). The ratio of coagulation factors V/II decreased intraoperatively and reached a minimum during the revascularization period, with no differences between the two groups. Postoperatively, most

Table 2. Preoperative coagulation parameters in groups C1 and A.

Coagulation test	*Group C1*	*Group A*	*p*
Hemoglobin (14-18 g/dL)	10.5±1.7*	11±1.4	n.s.
Platelets (150-400 x 10^9/L)	88±30.7	92±41	n.s.
Prothrombin activity (80-100%)	52±13.5	54.3±13.9	n.s.
aPTT (27-41 seg)	46.4±9	47.8±13.5	n.s.
Thrombin time (18-20 seg)	20.5±3.6	19.5±1.4	n.s.
Fibrinogen (150-400 mg/dL)	246±65.7	254±83	n.s.
Factor II (50-150%)	54.5±21	53±13	n.s.
Factor V (50-150%)	41±10	42.4±12	n.s.
Factor VII (50-150%)	45.4±10	46.9±9	n.s.
Factor X (50-150%)	64.2±10	63.3±13	n.s.
Factor VIII:C (50-150%)	85.6±18	82.4±14	n.s.
Factor IX (50-150%)	53.9±15	51±9	n.s.
Factor XI (50-150%)	50.8±9	50±14	n.s.
Factor XII (50-150%)	63.5±15	61.9±8	n.s.
Protein C (70-130%)	56.6±16	56±14	n.s.
Antithrombin III (80-120%)	61.8±11	57.7±17	n.s.
TAT complex (1-4 ng/mL)	14.4±10	13.9±12	n.s.
Plasminogen (80-120%)	68±21	65±18	n.s.
Antiplasmin (80-120%)	72±20.8	70±18	n.s.
t-PA (1-12 ng/mL)	15±9	15±8	n.s.
APP complex (80-470 mg/L)	262±80	250±75	n.s.
PAI 1 (4-43 ng/mL)	32±6	35±7	n.s.
D-dimer (0-25 ng/dL)	22.8±15	23±13	n.s.

**Mean±SD.*

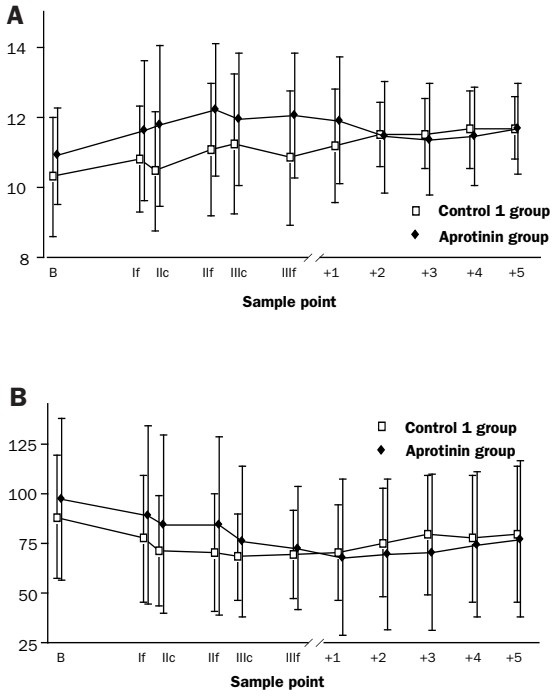

Figure 1. Changes in hemoglobin levels (A) and platelet count (B) (mean ± SD) during OLT and the first 5 days post-transplantant. p: n.s. vs group C1.

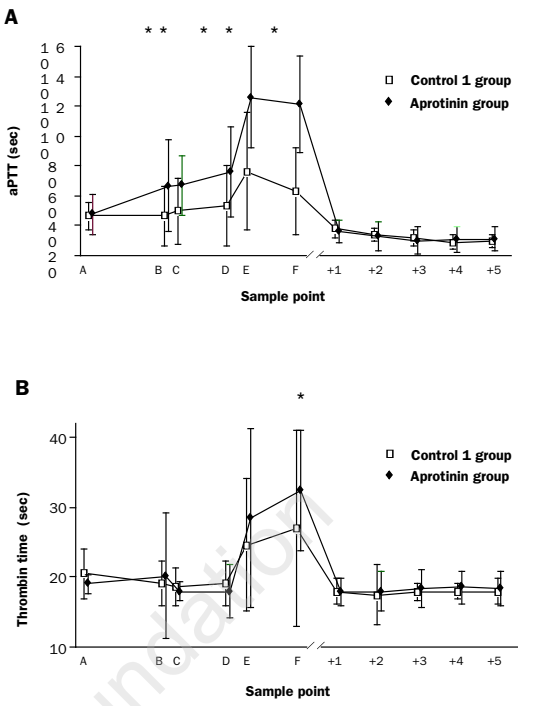

Figure 3. Changes in activated partial thromboplastin time (mean±SD). A) in thrombin time (mean±SD); B) during OLT and the first 5 days post-transplant.
*p<0.05 vs group C1.

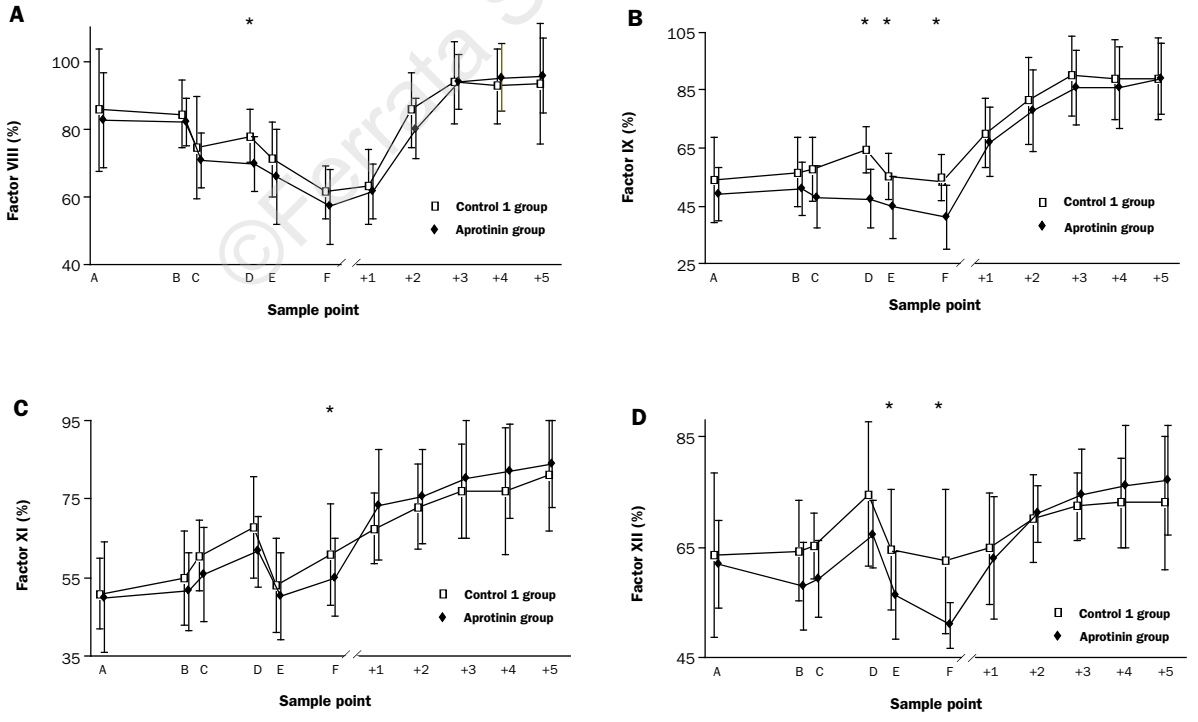

Figure 2. Changes in intrinsic pathway coagulation factor levels (mean ± SD) during OLT and the first 5 days posttransplantant. *p<0.05 vs group C1. (A) Factor VIII; (B) Factor IX; (C) Factor XI; (D) Factor XII.

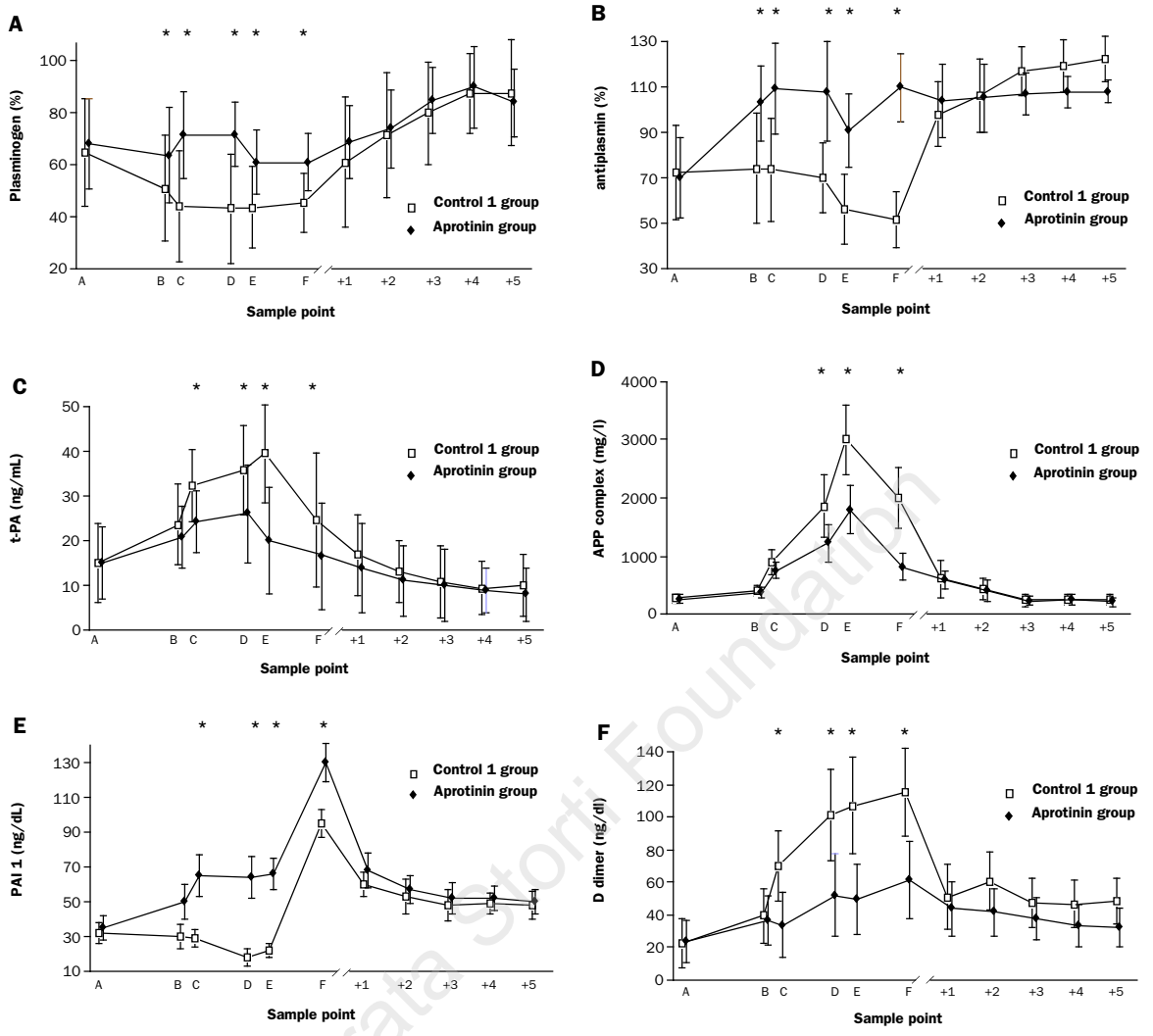

Figure 4. Changes in plasminogen (mean±SD). A) in antiplasmin activity (mean±SD); B), in t-PA levels (mean±SD); C), in APP complex (mean±SD); D), in PAI 1 levels (mean±SD); E) and in D dimer levels (mean±SD); F) during OLT and the first 5 days post-transplant. *p<0.05 vs group C1.

factors were within normal range from day +1; only factors V and VII remained lower and had not reached normal values by day +5.

A prolongation of aPTT was noticed in both groups after the beginning of surgery, more so in group A; it reached the maximum values at the beginning of graft reperfusion, and was significantly longer in group A ($p < 0.01$). Both groups had a normal aPTT value at the end of the surgical procedure and throughout the postoperative period (Figure 3). A similar course was observed for the TT, but there was only a slight difference between the two groups during the reperfusion phase ($p=0.09$) (Figure 3). The prolongation of TT was corrected by the addition of toluidine blue to the blood samples. No influence of aprotinin in TT was observed.

The PC and AT III activity and the concentration of the TAT complex were similar in both groups during the surgical procedure; at the end of surgery, we observed a significant increase in the TAT complex in group A compared to group C1 (156±41 ng/mL vs 113.9±35 ng/mL). The increase in the TAT complex was inversely correlated with the ratio V/II ($r= -0.9084$; $p= 0.012$) and with the AT III activity ($p= -0.49$: $p= 0.31$, ns). In the postoperative period, PC and AT III progressively recovered, reaching their maximum levels on day +5 in both groups A and C1. TAT complex values remained above normal in the early post-transplant days with no differences between the two groups (22±17 ng/mL in group C1 and 20±21 ng/mL in group A).

Results of the fibrinolytic assays

Preoperatively we observed an enhanced fibrinolytic activity in both groups C1 and A (Table 2). In group C1, PG and AP dropped progressively, reaching their lowest levels during the reperfusion phase. Therefore, in group A, PG remained near the basal levels until the reperfusion of the graft, and then rose slightly to 61±11% ($p < 0.05$), whereas AP activity reached higher levels than normal (> 100%) after aprotinin administration and throughout the surgical procedure ($p < 0.05$) (Figure 4). Antiplasmin activity was determined using different concentrations of aprotinin (25, 50, 100, 200, 300 and 400 KIU/ml) as samples, and we found a nearly linear correlation between the aprotinin concentration and antiplasmin activity. Thus, the higher AP levels in the aprotinin group are related to the antiplasmin effect of aprotinin in addition to the levels of intrinsic a2-antiplasmin. In both groups, PG and AP activity reached normal range on days +3 and +1, respectively.

Mean intraoperative levels of t-PA antigen and APP complex increased in groups A and C1 until the end of the anhepatic phase ($p < 0.05$) and both parameters reached their highest values after the reperfusion of the graft with the exception of t-PA in group A which dropped slightly ($p < 0.05$) (Figure 4). At the end of the surgical procedure, t-PA levels were near the normal values in group A but remained significantly higher in group C1 (Figure 4). T-PA was slightly elevated on day +1 in both groups, but it fell to normal range on day +2 in group A and on day +4 in group C1 ($p < 0.05$); APP complex showed normal levels in both groups at day +2.

During surgery, we observed a progressive drop of PAI 1 in group C1, from 30±7 ng/mL after the initial period to 18±5 ng/mL after the reperfusion of the graft; on the other hand PAI 1 remained above basal levels in group A ($p < 0.05$). PAI 1 rose beyond normal levels at the end of surgery in both groups ($p < 0.05$), and did not reach normal values at day +5 (Figure 4).

D-dimer increased in group C1 from the anhepatic phase onwards, peaking at the end of the reperfusion period (115±27 ng/dL). In group A, the mean D-dimer concentration was significantly lower during the anhepatic phase and did not peak during reperfusion (61.6±24 ng/dL) ($p < 0.05$). Thereafter, postoperatively, D-dimer was significantly lower ($p < 0.05$) in group A on days +1 and +2, and was slightly raised in both groups at day +5 (Figure 4).

Blood component transfusion

There were significantly lower transfusion requirements in group A, both in terms of the number of RBC and FFP units transfused during the surgical procedure ($p < 0.05$), and in the number of patients that did not require separate platelet transfusion ($p < 0.05$) compared to both groups C1 and C2 (Table 3). Finally, the only significant difference in blood requirements during the first 5 days of the postoperative period was in the number of patients who did not require RBC units: 80% in group A as compared with 55% in group C1 and 66.6% in C2 ($p = 0.04$).

Clinical evaluation

Mean time for the surgical procedure was longer in group C1 (7.7±2.5 h) and in group A (6±2 h) than in group C2 (4.8±1.6 h) ($p < 0.05$). There was a significant positive correlation between blood product requirement and length of surgery ($p = 0.001$) in groups C1 and C2 ($r = 0.74$ and $r = 0.67$, respectively), while it was not significant in the aprotinin group ($r = 0.23$; $p = 0.34$).

Average time to extubation and incidence of infectious complications in the early postoperative period were not different among the three groups (ns). Creatinine levels were similar in the three groups before and during the first month post-transplant (ns). No patients in the aprotinin group required a new laparotomy for postoperative hemorrhage compared to 4 and 3 patients in groups C1 and C2, respectively (ns). There were 4, 3 and 3 postoperative deaths during the first 30 days in groups A C1 and C2, respectively (ns). Patients who died in group C1 received a higher mean number of RBC units (50.6) than patients who survived (15 RBC units). No relation of this kind was observed in groups A and C2. No clinically important side effects, including thromboembolic complications, could be attributed to the high-dose aprotinin treatment.

Discussion

Whereas most groups have reported marked fibrinolytic activation in patients undergoing OLT and several studies have found that a high dose of aprotinin reduces blood loss in OLT, the effectiveness of this type of antifibrinolytic therapy is not well established.[14,16,17]

Our results show inhibition of hyperfibrinolysis in OLT and a significant reduction in blood requirements by the intraoperative administration of high-dose aprotinin in OLT. In most of the previous studies, a historical group of patients who had not received aprotinin was used as control group. In this study, we have introduced a second control group of patients who underwent liver transplantation after patients in the aprotinin group, which enable us to exclude improved perioperative management as the reason for the reduction in blood loss.

The antifibrinolytic effects of aprotinin were demonstrated by the significantly reduced t-PA, APP complex and D-dimer levels during the anhepatic and reperfusion phases in the treated group. These results suggest that aprotinin reduces t-PA release in OLT by inhibiting plasma kallikrein, as has been previously reported.[18-21] Nevertheless, Segal *et al*. observed that the activation of the contact system during OLT is

Table 3. Intraoperative blood requirements.

	Group C1 *n = 20*	*Group A* *n = 20*	*Group C2* *n = 30*	*p vs group C1*	*p vs group C2*
Red blood cells (units)	20.4±23.6* (4-105)° 15#	8.1±5.2 (0-22) 7	13±7.4 (2-30) 12.5	< 0.05	< 0.05
Fresh frozen plasma (units)	36±25.4 (11-103) 30	16.7±10.4 (0-40) 15	28±14 (0-58) 27	< 0.05	< 0.05
Platelets (units)	8.4±7.3 (0-26) 6	3±5 (0-14) 0	6±5.7 (0-27) 6	n.s.	n.s.
Patients receiving platelets units (%)	14 (70%)	7 (35%)	18 (60%)	< 0.05	< 0.05

**Mean±SD; °(range); #median. Mean an median blood usage are compared between groups A and C1 and between groups A and C2.*

minimal and that aprotinin does not alter the pattern of contact activation, despite its antikallikrein effect.[22]

In our patient group A, antiplasmin activity was above normal all throughout surgery following aprotinin administration. This was probably due to the antiplasmin effect of aprotinin shown in the antiplasmin assay, as well as to the intrinsic α_2-antiplasmin activity; thus, aprotinin might neutralize the plasmin produced by t-PA or kallikrein.[18,21,23] By inhibiting plasmin, aprotinin may prevent the inhibition of platelet function through the reduction of plasmin-generated fibrinogen degradation products.[24-26] However, the aprotinin effect on platelets was not analyzed in this study.

Compared to group A, group C1 patients had a slightly more evident fibrinolytic activation during the first five days post-surgery. This could explain persistent postoperative bleeding in some patients of group C1.

During surgery, and more so during the reperfusion of the graft, a marked impairment in hemostasis was noticed, including a decreased prothrombin activity, prolongation of aPTT and TT and a decrease in the coagulation factors and anticoagulant-proteins (AT III and PC). This is in broad agreement with previous findings.[4,5,27] The greater prolongation of aPTT and TT in group A at the anhepatic and the reperfusion phases could be explained by the known additive or synergistic effects of heparin and aprotinin, because both of them inhibit the contact phase of coagulation.[28] The presence of heparin in OLT may be, in principal, due to two facts: firstly, when veno-venous bypass is used in the anhepatic phase, a small dose of heparin is sometimes added to the bypass circuit; secondly, a moderate to severe heparin effect is seen in one-third of patients after reperfusion because of the release of heparin or heparin-like products from the graft.[11] In this study, no veno-venous bypass was carried out in any patient and the normalization of the prolonged TT with toluidine blue provides evidence of the presence of circulating heparin. Besides, we have observed that the greatest in vitro prolongation of TT in group A is not due to a direct aprotinin effect.

We noticed a generalized decrease in the coagulation factors level in both groups of patients, with no significant differences except in the intrinsic pathway factors (VIII, IX, XI and XII factors), which showed more prominent decreases in group A at the reperfusion phase. Inhibition of these factors by aprotinin has been reported, but this rarely happens at the concentration reached under clinical conditions.[13] It is possible that these results also reflect the synergism of aprotinin and heparin, since heparin inhibits these factors, too. Bellani *et al.* have related the bleeding taking place in OLT with the endogenous heparin which is released during the surgical procedure, not recognizing any important role for fibrinolytic or coagulation activation.[29] In spite of the above, some of the observed differences in coagulation parameters may have resulted from changes in either improved patient selection, improved organ preservation, or improved intraoperative technique.

Aprotinin usage reduced the intra- and post-operative blood requirements in our patient group A compared to groups C1 and C2. Since in our study, group A was followed by group C2, it is suggested that the lower blood requirements of group A patients was not only influenced by a better perioperative management, but also may explain the decrease in blood requirements in group C2 compared to C1. The lower group A transfusion requirements during surgery and the first 5 days post-transplant might correlate with a reduced fibrinolytic activation in this group due to the antifibrinolytic effect of aprotinin. This positive effect of aprotinin on blood loss is in agree-

ment with the findings of other authors which report mean transfusion requirements ranging from 7 to 8.2 RBC units, similar to our results (mean 8.4 RBC units).[14,16,17,19,20,30,31] On the other hand, our results contrast with those of other investigators who did not find a beneficial effect of aprotinin with respect to blood requirements.[18,32,33]

The aprotinin concentration required to inhibit plasmin activity (100 KIU/mL) appears to be lower than that required for *in vitro* inhibition of kallikrein (200 KIU/mL). Thus it is possible that a similar effectiveness could be achieved with aprotinin by targeting plasmin inhibition using a lower-dose regimen. We used the same high-dose aprotinin regimen employed by Hunt *et al.*;[18] a lower dose has resulted in a similar effectiveness, decreasing transfusion requirements,[34-36] but it is uncertain whether this smaller dose can be associated with lesser side-effects including thrombotic complications. There may be an association between aprotinin and thrombosis. Böhrer *et al.*[37] have reported rapid and unexpected thrombus formation on a pulmonary artery catheter in 3 patients given aprotinin during cardiac surgery and Baubillier *et al.*[38] reported a case possibly implicating aprotinin in the genesis of a pulmonary artery thrombosis during OLT. Further studies are necessary to document the incidence of such complications.

We observed no significant side-effects due to the use of aprotinin. There was a remarkably lower incidence of intra-abdominal bleeding requiring re-laparotomy in the aprotinin-treated patients, as reported by Neuhaus *et al.*[14] This might be related to the better hemostasis achieved with this antifibrinolytic agent. In contrast to other authors' reports,[16,17] we did not observe any significant influence of the use of aprotinin on postoperative morbidity, but the number of patients and the design in this study was defined in order to establish the impact of aprotinin on hemostasis and blood requirements during OLT. To obtain conclusions about morbidity, recruitment of a larger group of patients for randomized trials may be necessary.

The length of surgery was shorter in group C2 compared to groups C1 and A, and shorter in group A than in group C1. This has been attributed to the improvement in surgical and anesthetic management. Correlation was found between surgical time and the RBC and FFP units transfused in groups C1 and C2, but not in group A. These results suggest, firstly, that the shorter surgical time in group A cannot be attributed exclusively to aprotinin usage, but also to the better surgical technique and secondly, that the low blood requirements in group A were not related to the duration of surgery. Given the advances in surgical and anesthetic techniques and in the perioperative management, in our view, the use of aprotinin should be preferentially indicated in high risk patients potentially in need of higher blood requirements. Recently, it has been suggested that aprotinin may improve hemodynamic stability when administered during OLT.[39]

In this study, the prophylactic use of intraoperative high-dose aprotinin appears to be effective in reducing blood requirements in patients undergoing OLT. This has been shown to be related to its antifibrinolytic effect, which may be due to both antiplasmin and antikallikrein activities. Randomized trials are needed to establish the effectiveness of aprotinin in OLT and its optimal dosage. The observation by others that lower aprotinin doses are also useful in OLT deserves further evaluation.

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PLL was responsible for conception of the study, day-to-day contact with participants, coagulation measurements and data interpretations, data handling and writing of the paper. RC was responsible for the design of the study, supervision and counselling. JG-A was responsible for patient recruitment and critically revising the article for content. MNF was responsible for data interpretation and revising of manuscript content. The authors wish to thank Dra. Isabel Millán for the statistical analysis, Dr. V. Cuervas for enabling us to acquire clinical data.

Disclosures

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