The Prophylactic Use of Tranexamic Acid and Aprotinin in Orthotopic Liver Transplantation: A Comparative Study

Antonia Dalmau,[1] Antoni Sabaté,[1] Maylin Koo,[1] Carlos Bartolomé,[1] Antoni Rafecas,[2] Juan Figueras,[2] and Eduard Jaurrieta,[2]

The efficacy of tranexamic acid (TA) and aprotinin (AP) in reducing blood product requirements in orthotopic liver transplantation (OLT) was compared in a prospective, randomized and double-blind study. One hundred and twenty seven consecutive patients undergoing OLT were enrolled; TA was administered to 64 OLT patients at a dose of 10mg /kg/h and aprotinin was administered to 63 OLT patients at a loading dose of $2x10^6$ KIU followed by an infusion of 500,000 KIU/h. The portocaval shunt could not be performed in 14 OLT patients in the TA group and in 13 OLT patients in the AP group. However, all OLT patients that received either drug were included in the analysis. Perioperative management was standardized. Hemogram, coagulation tests, and blood product requirements were recorded during OLT and during the first 24 hours. No differences in diagnosis, Child score, preoperative coagulation tests, and intraoperative data were found between groups. No significant differences were observed in hemogram and intraoperative coagulation tests with the exception of activated partial thromboplastin time (aPTT). Similarly, there were no intergroup differences in transfusion requirements. Thromboembolic events, reoperations and mortality were similar in both groups. In conclusion, administration of regular doses of TA and AP during OLT did not result in large differences between the two groups. (*Liver Transpl 2004; 10:279–284.*)

Hyperfibrinolysis is a common feature of coagulopathy in patients with end stage liver disease, contributing to bleeding and increasing transfusion requirements during orthotopic liver transplantation (OLT). Kang reported that 82.5% of patients showed signs of hyperfibrinolytic activity in at least one blood sample during OLT.[1]

Aprotinin (AP) is a nonspecific serine protease inhibitor derived from bovine lung with a great affinity for plasmin and a lower affinity for kallikrein. It inhibits fibrinolysis and the inflammatory response, and it may be responsible for reducing platelet dysfunction.[2] Prophylaxis of hyperfibrinolysis with regular and high doses of AP has been reported as being effective when compared to a placebo in a multicenter study.[3] This study, however, raises questions concerning the variability in the contribution of the various surgical teams and techniques used. Another study, conducted in one center, showed that the prophylactic administration of low doses of AP reduced blood product requirements.[4]

Tranexamic acid (TA) is a synthetic derivative of the amino acid lysine. It exerts its antifibrinolytic effect through the reversible blockade of lysine binding sites on plasminogen molecules.[5] Prophylaxis of hyperfibrinolysis with TA has been reported to reduce transfusion requirements.[6] We have studied the prophylactic administration of TA in OLT and have reported its effectiveness and high degree of safety.[7,8] However, while both drugs have been reported as being effective, their respective efficacy has never been compared.

Materials and Methods

Population

Having been granted approval by the Institutional Review Board, written consent was obtained from all patients. A double-blind, prospective, randomized study was performed in all consecutive patients undergoing OLT from November 2000 to February 2003 in a single adult liver transplantation center. Our exclusion criteria were: 1) Budd-Chiari syndrome, 2) acute liver failure, 3) early retransplantation (less than one month), 4) simultaneous kidney and liver transplan-

Abbreviations: TA, tranexamic acid; AP, aprotinin; OLT, orthotopic liver transplantation; aPTT, activated partial tromboplastine time; FiO2, inspired oxygen fraction; RBC, packed red blood cells; FFP, fresh frozen plasma; INR, international normalized ratio; EACA, epsilonaminocaproic acid; ICU, intensive care unit; PT, prothrombin time; EHT, early hepatic thrombosis.

From the Department of [1]Anesthesiology and [2]Surgery, University Hospital of Bellvitge, Barcelona, Spain.

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Address reprint requests to A. Dalmau, c/Caldes 15-A. Sant Cugat. Barcelona 08190. Spain. Phone: 935893663. E-mail: antonia@altecom.es. Fax: 932607848.

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tation or renal insufficiency with dialysis, and 5) primary familial amyloidotic neuropathy.

Protocol

Participants were randomly assigned to either the TA or AP groups. Prophylaxis against allergic reactions was undertaken with 50 mg of ranitidine, 5 mg of dexchlorpheniramine and 0.5 mg/kg of methyl prednisone, administered intravenously before administration of TA or AP. Once anesthesia had been induced, patients in the TA group received a bolus of 250 ml of normal saline in 30 minutes followed by a continuous infusion of TA at a dose of 10 mg/kg/h, while patients in the AP group received a bolus of 2×10^6 KIU of AP in 250 ml of normal saline in 30 minutes followed by a continuous infusion of 500.000 KIU/h. Both drugs were diluted in normal saline in order to administer them at a rate of 100 ml/h after the bolus dose. Drugs were prepared using a randomization schedule provided in sealed envelopes. The anesthesiologist, nurse, and surgeons were unaware of the details of the randomization. All patients received drugs, via an infusion pump, from the induction of anesthesia until 2 hours after the portal vein was unclamped.

General anesthesia was induced with 2 mg/kg of propofol, 0.3 mg of fentanyl, and 0.6 mg/kg of rocuronium, and was maintained by continuous infusion of the same drugs. Mechanical ventilation was begun at 10 ml/kg with a respiration rate to obtain an end-expiratory partial pressure of CO_2 of 30–35 mmHg and an inspired oxygen fraction (FiO2) of 0.5 in air. Calcium and sodium bicarbonate were administered to maintain ionized calcium levels at approximately 1.2 mmol/L and to reach a pH greater than 7.30. A rapid infusion system attached to a 10 French catheter was used to infuse isotonic saline solution at a rate of 7–10 ml/kg/h. All patients were placed on a warm blanket (Warm Touch, Mallinckrodt Medical), their lower limbs were covered with cotton and aluminum foil and all intravenous fluids were administered through a fluid warmer.

Liver allografts were preserved using University of Wisconsin solution.[9] In all surgical procedures, a temporary portocaval anastomosis with preservation of vena caval flow was attempted.[10] OLT patients in whom the portocaval shunt could not be performed were included (an intention to treat analysis) to the final analysis of transfusion requirements and outcome. Prior to reperfusion of the graft, the liver was flushed with 1000 ml of Hartmann solution at 38°C in order to remove the air.

Criteria for Replacement Therapy

Packed red blood cells (RBC) were administered in order to maintain hematocrit levels at 30% and hemoglobin at 100 g/l. Fresh frozen plasma (FFP) was administered only when the international normalized ratio (INR) was 1.8. Platelets were administered to maintain a platelet count above 50×10^9/l and fibrinogen was administered to maintain fibrinogen levels above 1 g/l. No intraoperative salvage of blood was used during surgery.

Criteria for Pharmacologic Therapy

Sixty minutes before the procedure a single dose of desmopressin (4μg/kg in 100 ml of normal saline intravenously in 30 minutes) was given to all patients with a bleeding time over 8 minutes. Epsilon-aminocaproic acid (EACA) was administered at a dose of 0.25 g as a treatment of intraoperative clinical fibrinolysis (sudden diffuse bleeding not justified surgically, associated with fibrinogen values lower than 1 g/l).

Blood Analysis

Blood samples were taken before anesthesia induction, during dissection, during the anhepatic phase, 5 minutes after reperfusion of the graft, at the end of the surgical procedure, and in the intensive care unit (ICU) during the 24 hours after OLT. Arterial and venous mixed blood gases were obtained. All other samples were drawn through a central venous catheter unflushed by heparin. The following assays were performed: hemoglobin and hematocrit level, platelet count, prothrombin time (PT), activated partial thromboplastin time (aPTT), fibrinogen, ionized calcium, sodium, potassium, blood urea, creatinine, and blood glucose.

Data Collection and Endpoints

The primary endpoint of the study was the number of units of red blood cells (RBC) transfused throughout the procedure and during the first 24 hours in the ICU. The secondary endpoints were the number of units of fresh frozen plasma (FFP), platelets, and fibrinogen administered throughout the procedure and during the first 24 hours in the ICU. Other variables recorded included demographic data, cold ischemia time and other intraoperative data.

For postoperative outcome, our data analysis included all OLT patients that received any drug treatment. The data collected were the need for reoperation due to intra-abdominal bleeding, acute renal failure that required renal replacement therapy, and early ($\leq$ 30 days) postoperative vascular thrombotic complications. Systematic screening was performed for all patients with color pulsed doppler sonography (128×P/4, Acuson Computed Sonography, Mountain View, CA 940397393, USA) at the end of the procedure and in the first 24–48 hours to identify patency in all hepatic vessels. Doppler sonogram findings were considered abnormal when the signal was absent in either the main hepatic artery or in one of the intrahepatic branches. Arteriography with selective catheterization of the celiac axis was performed in these abnormal cases to confirm thrombosis of the hepatic artery. Mortality was also recorded: perioperative mortality being defined as death before discharge and 3 month mortality.

Statistical Analysis

The trial was designed to detect a 30% difference (1.8 units) in RBC requirements between groups, with a two-tailed alpha error of 0.05 and a beta error of 0.2, yielding a total sample size of 128 cases.

Replacement therapy is presented as means and standard deviation and median and percentile 25–75. Nonparametric

Table 1. Demographic and Intraoperative Data

	TA (n = 64)	AP (n = 63)
Age (years)*	53 (10)/54 (29-68)	54 (9)/57 (22-67)
Previous abdominal surgery†	15	18
Male/female†	45/19	44/19
Diagnostic†		
Cirrhosis	28	33
Cirrhosis-Hepatocarcinoma	25	22
Retransplantation	7	6
Others	4	2
Child-pugh Score†		
A (= 5-6 points)	17	16
B (= 7-9 points)	34	34
C (= 10-15 points)	13	13
Intraoperative data		
Graft cold ischemia (min)*	444 (154)	489 (161)
Duration anhepatic (min)*	63 (11)§	71 (15)§
Duration OLT (min)*	354 (74)	378 (71)
Reperfusion syndrome†‖	27	28

Abbreviations: TA = tranexamic acid, AP = aprotinin.
*Mean (SD)/median (range).
†χ^2 not significant.
§$P < 0.05$.
‖Reperfusion syndrome: 30% reduction of the blood pressure for more than 1 minute at the beginning of the reperfusion of the liver.

test (Mann-Whitney U) was used to compare groups. ANOVA was applied for intraoperative laboratory measurements. Discontinuous variables are presented in percentages and the χ^2 test was used to compare the groups. Differences with probability values of 0.05 or less were considered significant.

Results

One hundred and thirty seven OLTs were performed in the study. Ten patients were excluded because of primary amyloidotic neuropathy (3 cases), simultaneous kidney and liver transplantation (3 cases), acute hepatic failure (2 cases), and retransplantation (2 cases). One hundred and twenty-seven OLTs were included in the study and randomly assigned TA (64 OLTs) or AP (63 OLTs). It was not possible to use a porto-cava shunt in 14 OLTs belonging to the TA group and in 13 OLTs from the AP group.

There were no differences between treatment groups with respect to demographic data (Table 1) or baseline laboratory values (Table 2). The duration of anhepatic phase was longer in the AP group but not the duration of OLT (Table 1).

There was no statistical difference in preoperative desmopressin administration between both groups. It was undertaken in 82.8% (53/64 OLT) of cases in the TA group and in 85.7% (54/63 OLT) of the AP group.

The mean dose of total dose of tranexamic acid was 4.2 ± 1.3 gr (range 1.6–8.5 gr) and the mean of total dose of aprotinin was $5\times10^6 \pm 0.5\times10^5$ KIU (range 3.3×10^6 KIU–6.9×10^6 KIU).

Laboratory data and coagulation profiles are shown in Table 2. Coagulation tests showed changes over time during the procedure, but there were no significant intergroup differences. Only the aPTT during the operation was significantly higher in the AP group throughout the procedure. This effect, however, disappeared in the first 24 hours after the procedure.

Intraoperative transfusion requirements, intraoperative fluid therapy, and transfusion in the first 24 hours did not differ between the two groups (Table 3). Twenty six OLTs (46%) in the TA group and 23 OLTs (36.5%) in the AP group did not require RBC transfusion.

EACA (for the treatment of clinical hyperfibrinolysis) was only administered in the case of one patient in the AP group. This patient had a moderate pulmonary hypertension that was treated with prostaglandin. He then lost a large amount of blood during the hepatectomy because of technical problems and during the early reperfusion period he developed a serious pulmonary hypertension that was, however, under control by the end of the procedure.

Perioperative outcome is shown in Table 4. No allergic reactions and no differences in the postoperative events between both groups were reported. In the TA

Table 2. Laboratory Measurements

	Baseline	Disection	Anhepatic	Reperfusion	End of Procedure	24h ICU
Hb (g/l)						
Tranexamic acid	11.58 (2.2)	10.09 (2.3)	10.21 (2)	9.88 (1.9)	10.33 (1.5)	10.76 (1.8)
Aprotinin	11.49 (2.1)	10.34 (1.9)	10.26 (1.8)	9.92 (1.6)	10.24 (1.5)	10.71 (1.5)
Platelets ($\times 10^9$/l)						
Tranexamic acid	98 (69)	100 (59)	99 (51)	89 (40)	87 (50)	72 (48)
Aprotinin	96 (53)	109 (44)	101 (45)	87 (38)	86 (42)	69 (27)
INR						
Tranexamic acid	1.37 (0.26)	1.55 (0.31)	1.61 (0.35)	2.07 (0.63)	2.13 (0.67)	1.60 (0.45)
Aprotinin	1.42 (0.39)	1.55 (0.36)	1.66 (0.35)	2.02 (0.65)	2.18 (0.59)	1.47 (0.29)
aTTP (ratio)						
Tranexamic acid	1.26 (0.31)	1.55 (0.62)*	1.40 (0.33)*	2.65 (1.57)*	1.77 (0.65)*	1.23 (0.21)
Aprotinin	1.21 (0.27)	2.02 (0.91)*	2.11 (0.85)*	4.10 (1.89)*	2.33 (0.80)*	1.20 (0.18)
Fibrinogen (g/l)						
Tranexamic acid	3.08 (1.70)	2.52 (1.39)	2.36 (1.19)	1.97 (1.13)	2.03 (1.06)	3.47 (1.05)
Aprotinin	3.09 (1.33)	2.56 (1.04)	2.40 (0.97)	1.95 (0.89)	1.99 (0.92)	3.51 (1.09)

Values refers as mean ± SD.
*$P < 0.05$.
Abbreviations: Hb, hemoglobin; INR, international normalized ratio; aTTP, activated partial tromboplastin time.

group, four patients presented thrombosis: two patients had hepatic artery thrombosis (one underwent retransplantation whereas the other presented the thrombosis after developing multiorgan failure and died), one patient suffered an acute myocardial infarction in the 12th postoperative day (he had a asymptomatic coronariopathy, he was discharged and he died because of the recurrence of myocardial infarction) whereas the last patient had a jugular thrombosis because of the rupture of the Swan-Ganz catheter (successfully treated without any residual lesion). In the AP group, two patients presented thrombosis: one patient suffered stenosis of the hepatic artery and liver infarction with no repercussions on the hepatic function, while the other

Table 3. Replacement Therapy

	TA (n = 64) Mean (SD)/Median [p. 25-75]†	AP (n = 63) Mean (SD)/Median [p. 25-75]†	*P*
Intraoperative			
RBC (units)	2.14 (2.32) / 2 [0-4]	2.44 (3.03) / 2 [0-4]	NS
FFP (units)	1.20 (2,21) / 0 [0-2]	1.09 (2.20) / 0 [0-2]	NS
Platelet	4.92 (5,89) / 4.5 [0-9.75]	5.44 (6.15) / 5 [0-10]	NS
Fibrinogen*	1 / 64 (1.6%)	3 / 50 (4.8%)	NS
Crystalloid and colloid (ml)	4731 (2703)	4643 (1880)	NS
24 h postoperative			
RBC (units)	0.87 (2.60) / 0 [0-0]	0.86 (1.77) / 0 [0-1]	NS
FFP (units)	0.86 (1.65) / 0 [0-2]	1.16 (2.11) / 0 [0-2]	NS
Platelet (units)	1.22 (4.39) / 0 [0-0]	0.76 (2.56) / 0 [0-0]	NS
Fibrinogen*	1 / 64 (1.6%)	0	NS
Total			
RBC (units)	3.02 (3.79) / 2 [0-4]	3.30 (4.16) / 2 [0-4]	NS
FFP (units)	2.03 (2.96) / 0 [0-4]	2.22 (3.61) / 0 [0-4]	NS
Platelet (units)	5.98 (7.59) / 4.5 [0-10]	5.70 (6.32) / 5 [0-10]	NS
Fibrinogen*	2 / 64 (3.12%)	3 / 63 (4.76%)	NS

Abbreviations: TA, tranexamic acid; AP, aprotinin; RBC, red blood cells; FFP, fresh frozen plasma.
*Test χ^2.
†Values expressed as standard deviation/median [p. 25-75] = percentile 25-75.

Table 4. Postoperative Outcome

	TA (n = 64)	AP (n = 63)	χ^2
Thrombosis	4 (6.25%)	2 (3.17%)	NS
Reoperation			
Bleeding	2 (3.12%)	2 (3.17%)	NS
Retransplantation*	1 (1.56%)	0	NS
Renal failure†	4 (6.25%)	2 (3.17%)	NS
Mortality perop	3 (4.69%)	0	NS
Mortality	4 (6.25%)	1 (1,59%)	NS

Abbreviations: TA, tranexamic acid; AP, aprotinin.
*Retransplantation due to arterial hepatic thrombosis.
†Renal failure with renal replacement therapy.

patient's left portal thrombosis was successfully treated with anticoagulation.

Discussion

In this study the administration of TA, on the one hand, and AP, on the other, resulted in transfusion rates without any significant differences being recorded between the two groups. Although the duration of anhepatic phase was longer in the AP group, this would not seem to have influenced the results as all the baseline characteristics (demographic data, preoperative laboratory values and intraoperative data) did not differ, showing the two groups to be comparable.

The percentage of patients that received desmopressin was high in both groups, as bleeding time was longer than 8 minutes in most of patients, and desmopressin may shorten bleeding time in liver cirrhosis.[11] Desmopressin was administered 60 minutes before surgery in order to achieve peak plasma level at the time of anesthesia induction and monitoring of patient. This dose should not influence hemostasis during the surgical procedure, as redistribution of factor VIII to storage sites produces a terminal half-life of desmopressin of 4 hours.[12]

Similarly, there were no intergroup differences in hemoglobin, platelets, INR, and fibrinogen levels throughout the OLT and in the first 24 hours. aPTT was significantly higher in the AP group throughout the procedure, an effect described elsewhere[2] and also described in the European Multicenter Study,[13] although in the study reported by Findlay et al. this was not demonstrated.[4]

In our 1993 study,[14] aprotinin was not more effective than a placebo. Mixed surgical procedures (piggyback technique, venovenous by-pass, or venous cava clamp) made comparison difficult. Improvements in surgical techniques, anesthesiological care, and organ preservation have contributed greatly to the reduction in transfusion requirements making it difficult to compare earlier research findings with present studies.

TA has previously been reported as being effective in reducing transfusion requirements either in high doses or in regular doses.[6,7] In this study, the transfusion rates are even better than those described previously by our group,[7,8] AP has also been reported to reduce transfusion requirements in two controlled studies with different doses.[3,4]

The most dangerous complication associated with the administration of antifibrinolytics is thrombosis. Indeed, there have been case reports of thromboembolic complications related to the administration of high doses of epsilon-aminocaproic acid.[15] Similarly, AP administration has been associated with thrombosis in over transfused patients or when administered with high doses of epsilon-aminocaproic acid.[16–19] In the present study, we found no intergroup differences. In the case of TA, hepatic artery thrombosis with TA (3.12%) was comparable to that reported in our previous study (4.9%).[8] The study by Boylan et al., using high doses of TA,[6] did not report any case of thrombosis, though they did not undertake a systematic screening for it and they also administered a solution of dipyridamole-heparin for thrombosis prophylaxis. In the case of AP, the incidence of thrombosis in the present study with AP (3.17%) is similar to that reported in Porte et al.[3] in which two cases (4.4%) of thrombosis were found in the high-dose group, none in the regular-dose group, and three cases (6.25%) in the placebo group. Findlay et al. described one case (3.03%) of hepatic thrombosis using low doses of AP and two cases (6.6%) of hepatic thrombosis in the placebo group. In a study with a large series of OLT patients, where systematic screening for early hepatic thrombosis (EHT) was used, there were 17 OLTs with EHT (6%).[20] A figure similar to the one found in the present study: two OLTs in the TA group (3.12%) and one patient in the AP group (1.58%).

Renal dysfunction is a further side effect associated with the use of antifibrinolytics. Here, there was no difference in renal replacement therapy in the two groups. Indeed, the percentage is lower than that reported in other series of OLTs.[21]

Both drugs, tranexamic acid and aprotinin, are generally avoided in those patients with preoperative thrombosis (Budd-Chiari syndrome, hepatic artery or portal venous thrombosis) and those with coexisting disease at thrombotic risk (ischemic myocardiopathy, vascular cerebral accident), so that in the study protocol Budd-Chiari patients are always excluded.[3,7,8,14]

Presently, we choose to administer tranexamic acid

in the prophylaxis of hyperfibrinolysis during OLT because it is less expensive and fewer case reports of allergic reactions have been described when using it. However, we continue to administer aprotinin when tranexamic acid has been previously used. We treat ongoing bleeding due to hyperfibrinolysis with a low dose of EACA (250–500 mg) as established by Kang et al.,[1] though such treatment at our center is rare (less than 1%). At the same time, we only administer FFP when the patient is actively bleeding and the prothrombin time is considerable.

However, aprotinin is a broad spectrum serine protease inhibitor with an anti-inflammatory effect that may have beneficial effects on hemodynamics during liver transplantation and on early graft function. In one study patients treated with aprotinin required less vasoactive intervention.[22] Also, patients treated with aprotinin showed higher one-month survival when compared to placebo.[23] If confirmed by further studies, these collateral beneficial effects of aprotinin should be taken into consideration to establish routine administration of this drug in liver transplantation.

We conclude that in our study large differences are not likely to occur between the administration of both TA and AP in regular doses in relation to blood product requirements during OLT.

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