ORIGINAL ARTICLE

Aprotinin and the Risk of Thrombotic Complications After Liver Transplantation: A Retrospective Analysis of 1492 Patients

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Aprotinin is an antifibrinolytic drug that reduces blood loss during orthotopic liver transplantation (OLT). Case reports have suggested that aprotinin may be associated with an increased risk of thromboembolic complications. Recent studies in cardiac surgery also have suggested a higher risk of renal failure and postoperative mortality. Despite these concerns, no large-scale safety assessment has been performed in OLT. In a retrospective observational study involving 1492 liver transplants, we studied the occurrence of postoperative thromboembolic or thrombotic events and mortality in patients who received aprotinin (n = 907) and patients who did not (n = 585). The overall incidence of hepatic artery thrombosis and central venous complications (pulmonary embolism or inferior vena cava thrombosis) was 3.2% and 0.9%, respectively. In propensity score–adjusted analyses (C-index = 0.79), aprotinin was not associated with an increased risk of hepatic artery thrombosis [odds ratio (OR) = 1.00, 95% confidence interval (CI) = 0.50-2.01, $P = 0.86$]. Although central venous complications were found more frequently in patients receiving aprotinin, the difference was not statistically significant (OR = 2.95, 95% CI = 0.54-16.23, $P = 0.32$). In addition, no significant differences were found in 1-year mortality (OR = 1.21, 95% CI = 0.86-1.71, $P = 0.32$). In conclusion, this study did not demonstrate an increased risk of thrombotic complications or mortality when aprotinin is used during OLT. ***Liver Transpl 15:747-753, 2009.*** © **2009 AASLD.**

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Orthotopic liver transplantation (OLT) is a major surgical procedure that historically has been associated with a risk of massive intraoperative blood loss.[1,2] The cause of increased bleeding during OLT is multifactorial.[3,4] Besides the obvious relationship between surgical skills and perioperative blood loss, specific intraoperative disturbances in the hemostatic system, such as hyperfibrinolysis, have been identified as important causes of nonsurgical bleeding in these patients.[4,5] During the last decade, blood loss and transfusion requirements have decreased gradually because of increasing experience, improvements in surgical and anaesthetic methods, and the use of antifibrinolytic drugs such as aprotinin.[6]

Aprotinin is a natural polypeptide derived from bovine lung and a serine protease inhibitor. It has the ability to reduce fibrinolysis by inhibiting the action of a wide range of serine proteases, including plasmin and kallikrein.[7] In several randomized controlled trials, aprotinin has been shown to reduce intraoperative

Abbreviations: CI, confidence interval; HAT, hepatic artery thrombosis; HBV, hepatitis B virus; HCV, hepatitis C virus; INR, international normalized ratio; IVCT, inferior vena cava; MELD, Model for End-Stage Liver Disease; OLT, orthotopic liver transplantation; OR, odds ratio; PBC, primary biliary cirrhosis; PE, pulmonary embolism; PSC, primary sclerosing cholangitis; SBC, secondary biliary cirrhosis; TE, thromboembolism; VVB, venovenous bypass.

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blood loss in patients undergoing liver transplantation by 30% to 50%.[8-10]

Case reports, however, have pointed toward an important safety concern: the potential higher risk of thromboembolic complications.[11-13] Recently, the use of aprotinin in patients undergoing cardiac surgery has even been associated with a higher risk of renal failure and postoperative mortality.[14-16] In liver transplantation, a recent meta-analysis of randomized controlled trials did not provide evidence for an increased risk of thromboembolic events or postoperative mortality associated with antifibrinolytic drugs.[17] This meta-analysis, however, included studies that were not primarily designed to study thromboembolic complications, and meta-analyses are often limited by the heterogeneity of patient populations and variations in drug dosing. Moreover, randomized controlled trials are usually performed in selected patient populations with a relatively low risk profile for postoperative complications. To investigate the impact of aprotinin on the occurrence of thromboembolic complications in everyday practice, we studied a large series of patients from 3 participating European centers who underwent liver transplantation.

PATIENTS AND METHODS

Study Population

Patients undergoing liver transplantation at the Royal Free Hospital in London, Addenbrooke's Hospital in Cambridge, or the University Medical Center in Groningen between January 1994 and December 2004 were included in this study. Excluded were children (≤17 years), patients undergoing retransplantation or combined organ transplantation, and patients receiving a split or reduced-size liver graft. In addition, patients who received other antifibrinolytic drugs, such as tranexamic acid, were excluded from this study. The population could be divided into 2 eras: patients who were transplanted between 1994 and 1998 and transplant recipients between 1999 and 2004. In the 3 centers, patient characteristics, demographic variables, perioperative clinical variables, and postoperative outcomes are prospectively collected in an institutional liver transplant database. These computer databases are maintained by dedicated scientific personnel and are regularly validated. Data from these observational databases were used for the current analysis. Missing variables were completed from the medical records if possible.

Transplants were performed with either the conventional technique (with or without the use of venovenous bypass) or the piggyback technique with preservation of the recipients' inferior vena cava (IVC). The use of venovenous bypass was dependent on the consultant anesthetist and surgeon. Aprotinin (Trasylol, Bayer AG, Wuppertal, Germany) was administered according to institutional guidelines and independently of the attending surgeon. At the Royal Free Hospital, prophylactic use of aprotinin was generally recommended in all patients except those with cholestatic liver disease. At Addenbrooke's Hospital, aprotinin was given to all patients except those with cholestatic liver disease and normal coagulation screening tests or a preexisting thrombotic condition. At the University Medical Center in Groningen, aprotinin was recommended in all patients undergoing liver transplantation, except for patients with known thrombophilia or preexisting thrombotic conditions or signs of hypercoagulability on thromboelastography at the time of induction of anesthesia. Based on evolving scientific evidence concerning the efficacy of aprotinin,[10,18] guidelines were slightly modified during the study period. Aprotinin was in all 3 centers administered intravenously as follows: 2×10^6 kallikrein inhibiting units over 30 minutes after induction of anesthesia followed by a continuous infusion of 0.5×10^6 kallikrein inhibiting units per hour during the procedure. The infusion of aprotinin was stopped 2 hours after reperfusion of the donor liver.

Postoperative Management

Patency of the liver graft vessels was checked regularly during the first postoperative week with Doppler ultrasound. After the first week, Doppler ultrasound was performed in the event of a rise in serum liver enzymes or any other clinical suspicion of a thrombotic complication. The diagnosis of hepatic artery thrombosis was always confirmed by conventional angiography or computed tomography angiography. Pulmonary embolism (PE) or IVC thrombosis was detected by computed tomography angiography or a pulmonary perfusion scan performed in case of clinical symptoms. In some patients, partially occluding thrombi of the central venous system were found incidentally during imaging studies performed for another reason.

Data Collection

The following variables were included in this analysis: center and era of transplantation; recipient age and gender; indication for transplantation; preoperative serum creatinine, albumin, and total bilirubin levels; international normalized ratio of the prothrombin time and Model for End-Stage Liver Disease (MELD) score; intraoperative use of venovenous bypass and use of aprotinin; and total (cold and warm) ischemia time of the donor liver. Primary endpoints in this study were the occurrence of hepatic artery thrombosis and central venous thromboembolic complications within 30 days after surgery and mortality within 1 year after transplantation. Central venous thromboembolic complications were defined as either pulmonary embolism or (partial or complete) thrombosis of the IVC.

Statistical Analysis

Statistical analysis was performed with the SPSS/PC Advanced Statistics Package, version 12.0 (SPSS, Chicago, IL). Categorical variables are presented as numbers with percentages, and continuous variables are

presented as medians and interquartile ranges. Baseline and postoperative differences between groups were compared with Pearson's chi-square test or Fisher's exact test for categorical variables and with the Mann-Whitney U test for continuous variables. Actual 1-year patient survival rates were calculated and compared with Pearson's chi-square test.

Because treatment assignment was not based on random allocation and the 2 groups (aprotinin versus no aprotinin) were therefore not expected to be comparable with respect to important covariates, propensity score stratification was used to control for these differences. To identify variables that were unbalanced between patients who received aprotinin and those who did not, univariate comparison was performed for all potential confounding covariates that could potentially affect treatment decisions.[19] A stepwise multiple logistic regression model was then fit with covariates with a P value ≤ 0.10 to determine important predictors of treatment selection. A model, which consisted of 8 variables including center, era, age and gender of the recipient, indication for transplantation, and preoperative serum creatinine, bilirubin, and international normalized ratio, was subsequently used to calculate the propensity score for each individual patient. The area under the receiver operating characteristic curve (C-index) for this model was 0.79, indicating good discrimination between patients receiving aprotinin and those not receiving aprotinin. Patients were then sorted by propensity score and clustered into quintiles accordingly. After stratification by propensity score, the 2 groups were again compared for all covariates with the Cochran-Mantel-Haenszel chi-square test and 2-way analysis of variance to identify any remaining bias. The effect of aprotinin on each endpoint was then analyzed within each quintile. The Mantel-Haenszel odds ratio (OR), representing a composite of the 5 ORs derived from each quintile, was calculated in addition to the Cochran-Mantel-Haenszel chi-square. Statistical tests were assumed to have reached significance at the conventional level of 0.05.

RESULTS

Patient Characteristics

A total of 1492 liver transplant recipients, transplanted between January 1994 and December 2004, met the study criteria and were included. Patient characteristics as well as surgical variables of the entire group are summarized in Table 1. Intraoperative prophylaxis with aprotinin was given to 907 patients (60%), whereas 585 patients (40%) did not receive aprotinin. Because treatment assignment was not based on random allocation, large differences were noted in perioperative variables between the 2 groups. These differences were adequately corrected after propensity adjustment (Table 1). Only the MELD score and recipient age remained significantly different between the 2 groups. However, the median MELD scores were similar in the 2 groups, and the absolute difference in age was small and did not appear to be clinically relevant.

Intraoperative Use of Aprotinin and Postoperative Thrombotic Complications

The overall incidence of hepatic artery thrombosis was 3.2%, and the incidence of central venous thromboembolic complications (PE or IVCT) was 0.9%. The incidence of hepatic artery thrombosis was higher (3.5% versus 2.6%) and venous thromboembolism was greater (1.2% versus 0.3%) in aprotinin-treated patients, but this did not reach statistical significance (Fig. 1). Of all patients, 215 (14.4%) died within 1 year after transplantation. There was no significant difference in the unadjusted 1-year mortality rate between the 2 groups (Fig. 1).

As was noted previously, the 2 groups were not completely comparable at baseline. We, therefore, reanalyzed the risk of thromboembolic complications after propensity score stratification (Table 2). There was no significant difference in the risk of developing hepatic artery thrombosis in patients who had received aprotinin and those who had not [OR = 1.00, 95% confidence interval (CI) = 0.50-2.01, P = 0.86]. In addition, no significant differences were found in the risk of venous thromboembolic events (OR = 2.95, 95% CI = 0.54-16.23, P = 0.32) or in 1-year patient mortality (OR = 1.21, 95% CI = 0.86-1.71, P = 0.32) between the 2 groups (Table 2).

DISCUSSION

In this large, retrospective, observational study of 1492 adults undergoing OLT for the first time, intraoperative treatment with aprotinin was not associated with a significantly increased risk of postoperative thromboembolic events in comparison with controls. Moreover, no significant differences were found in the mortality rate within 1 year after transplantation between patients who received aprotinin and patients who did not.

The efficacy of aprotinin in reducing blood transfusion requirements during OLT has been demonstrated in multiple randomized controlled trials.[10,18] Recently, however, it has been debated whether aprotinin may be associated with important side effects, such as thromboembolic complications or renal failure, in cardiac surgery patients.[12,20] In patients undergoing cardiac surgery, retrospective studies have even suggested a higher risk of postoperative mortality when aprotinin was given.[15,16]

In liver transplantation, the debate on the clinical safety of aprotinin has been primarily fed by case reports of patients developing an intraoperative PE and/or intracardiac thrombosis when aprotinin was given. A recent review of 74 cases of PE and/or intracardiac thrombosis in patients undergoing liver transplantation apparently showed that these thrombotic complications can occur in both patients who receive aprotinin and those who do not, leaving undetermined whether aprotinin is associated with an increased risk or not.[21] Compared to venous thromboembolic complications, hepatic artery thrombosis is far more common after liver transplantation. The incidence reported in

TABLE 1. Characteristics of the Entire Study Population

Variable	Total Population (n = 1492)	No Aprotinin Use [n = 585 (40%)]	Aprotinin Use [n = 907 (60%)]	*P* Value*	*P* Value†
Center					
I	593 (40%)	111 (19%)	482 (53%)	<0.001	0.54
II	302 (21%)	198 (34%)	104 (12%)	<0.001	0.57
III	597 (40%)	276 (47%)	321 (35%)	<0.001	0.99
Era				<0.001	0.22
I	820 (55%)	405 (69%)	415 (46%)		
II	672 (45%)	180 (31%)	492 (54%)		
Age (years)	51 (42-58)	50 (39-57)	58 (44-58)	0.002	<0.001
Gender				0.003	0.99
Male	874 (58%)	315 (54%)	559 (62%)		
Female	618 (42%)	270 (46%)	348 (38%)		
Diagnosis					
Biliary cirrhosis	340 (23%)	178 (30%)	162 (18%)	<0.001	0.78
PBC	180	90	90		
PSC	153	84	69		
SBC	7	4	3		
Postnecrotic cirrhosis	913 (61%)	288 (49%)	625 (69%)	<0.001	0.56
HBV	110	31	79		
HCV	287	64	223		
Alcoholic	270	83	187		
Cryptogenic	109	50	59		
Autoimmune	62	32	30		
α-1-Antitrypsin deficiency	21	10	11		
Cirrhotic other	54	18	36		
Acute liver failure	120 (8%)	47 (8%)	73 (8%)	0.99	0.95
Miscellaneous	119 (8%)	72 (12%)	46 (5%)	<0.001	0.63
Preoperative serum creatinine (mg/dL)	0.95 (0.81-1.18)	0.93 (0.76-1.15)	0.99 (0.83-1.20)	<0.001	0.57
Preoperative serum bilirubin (mg/dL)	2.98 (1.52-6.67)	3.28 (1.52-7.62)	2.81 (1.46-6.08)	0.06	0.20
INR	1.5 (1.2-1.9)	1.4 (1.2-1.8)	1.5 (1.3-1.9)	<0.001	0.18
MELD	15 (11-21)	15 (11-20)	15 (12-21)	0.03	0.04
Technique				0.21	0.41
With VVB	365 (25%)	145 (25%)	220 (24%)		
Without VVB	1071 (72%)	386 (66%)	685 (76%)		
Total ischemia time (minutes)	669 (533-797)	665 (514-795)	672 (541-799)	0.27	0.17

NOTE: Data are reported as median (interquartile range) or number (proportion).
Abbreviations: HBV, hepatitis B virus; HCV, hepatitis C virus; INR, international normalized ratio; MELD, Model for End-Stage Liver Disease; PBC, primary biliary cirrhosis; PSC, primary sclerosing cholangitis; SBC, secondary biliary cirrhosis; VVB, venovenous bypass.
**P* values are for the comparison between patients treated with aprotinin and patients not treated with aprotinin.
†*P* values are those calculated after adjustment according to propensity score stratification.

the literature varies from 1.8% to 9.0%.[22,23] In particular, hepatic artery thrombosis occurring early after OLT is a serious complication that may result in biliary strictures due to bile duct ischemia or even graft failure.[24] In the current study, we focused on the occurrence of hepatic artery thrombosis within 30 days after transplantation because we felt it unlikely that a drug such as aprotinin, which is given only intraoperatively, would have an impact at a longer time interval after transplantation. The observed incidence of (early) hepatic artery thrombosis in the current study was 3.2%, and this is in accordance with data published by others.[17,22] The propensity-adjusted risk of postoperative hepatic artery thrombosis was not increased in patients who had been given aprotinin during the transplant procedure. This finding is in accordance with a recent meta-analysis of prospective studies focusing on the safety and efficacy of antifibrinolytic drugs in liver transplant recipients.[17]

Venous thromboembolic complications, such as thrombosis of the vena cava or PE, are rarely seen in patients undergoing liver transplantation, and the exact incidence is unknown. It has been suggested that the occurrence of intraoperative PE is underestimated, and some authors have indicated that this type of thromboembolic complication may occur in up to 1% of patients.[25,26] In 1 series, the incidence of postoperative PE was reported to be 1%,[27] and postoperative throm-

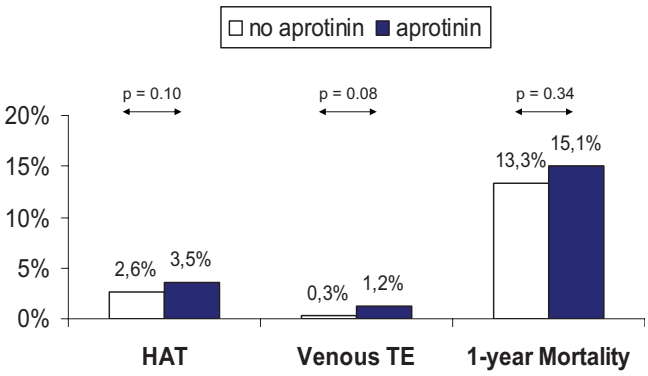

Figure 1. Unadjusted comparison of the rates of postoperative hepatic artery thrombosis (HAT), venous thromboembolism (TE), and 1-year mortality in liver transplant recipients who were given aprotinin and those who did not receive aprotinin during the procedure. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com]

TABLE 2. Propensity Score–Adjusted Risk of Postoperative Thromboembolic Events and Mortality in Patients Who Received Aprotinin Compared to Controls

Outcome Event	Odds Ratio (95% Confidence Interval)	*P* Value
Hepatic artery thrombosis	1.00 (0.50-2.01)	0.86
Venous thromboembolic events*	2.95 (0.54-16.23)	0.32
1-year patient mortality	1.21 (0.86-1.71)	0.32

*Venous thromboembolic events include pulmonary embolism and inferior vena cava thrombosis.

bosis of the IVC has been described in up to 2.5%.[28] Although these events are infrequent, they are not infrequently lethal.[21]

In the current study, the overall incidence of postoperative central venous thromboembolic events was 0.9%. The unadjusted analysis showed a 4-fold higher incidence of venous thrombotic complications in patients who had received aprotinin versus those who had not, and this was borderline statistically significant. In the propensity-adjusted analysis, the use of aprotinin was associated with a 2.95-fold higher risk of central venous thromboembolism. Although this again was not statistically significant, these findings may carry some message, and possibly the size of the current study cohort was not large enough to demonstrate statistical significance. In the light of these findings, it is relevant to realize that arterial thrombosis and venous thrombosis are believed to have different pathogeneses. Although primary hemostasis and blood platelets have been identified as critical factors in the development of arterial thrombosis, the plasmatic coagulation cascade is believed to be more relevant in the pathogenesis of venous thrombosis. Apart from its strong antifibrinolytic properties, aprotinin has been shown to exhibit an antiplatelet effect.[29] In addition, aprotinin has an inhibiting effect on the plasmatic coagulation cascade, as reflected by a prolongation of the activated partial thromboplastin time and the *r* value in thrombelastography.[30] Despite the antiplatelet and anticoagulant effects, the antifibrinolytic capacity of aprotinin might be a greater risk factor for venous thrombotic events than for arterial thrombosis. More research in the area seems warranted.

The lack of significant differences in thromboembolic events does not necessarily mean that there is no increased risk associated with the use of aprotinin in individual patients. Some investigators have warned against using prophylaxis with antifibrinolytic drugs for patients with a (nearly) normal coagulation profile or with signs of hypercoagulability either before or during OLT.[20,31] Moreover, it is becoming clear that not all patients with end-stage liver cirrhosis suffer from hypocoagulability, as traditionally believed, and some in fact have signs of hypercoagulability.[32-34] Several recent studies have shown that liver cirrhosis is often associated with hypercoagulation rather than hypocoagulation, and patients with cirrhosis are not exempt from developing thromboembolic complications.[21,35,36] Better identification of such patients may have an important impact on the safety margins of any prohemostatic drug.

A limitation of the current study is its retrospective and nonrandomized design. However, the results of the current study are in accordance with those of prospective clinical studies.[10,18] We have used propensity score adjustment, which is currently considered to be the most robust statistical method available to control for selection bias with respect to the use of specific medications.[37,38] The propensity score is defined as the conditional probability of being treated given the individual's covariates. Once estimated, the propensity score can be used to reduce bias through matching, stratification, or regression adjustment. We used stratification based on propensity scores, which has been proposed as a robust application of the propensity score.[37,38] The C-index for the propensity scores in our study was 0.79, indicating good discrimination between patients receiving aprotinin and patients receiving no aprotinin. When the 2 groups were compared prior to propensity adjustment, significant differences were found at baseline for various covariates. Re-analyses of baseline characteristics after propensity score–based stratification demonstrated that the preexisting differences in covariates were adequately controlled, and this allowed a meaningful comparison of outcome data.

An advantage of the current study is that it represents daily practice. The aim of the current study was not to identify risk factors for the development of thrombotic complications after OLT. Several previous studies have focused on the identification of risk factors for hepatic artery thrombosis.[22-24] These studies have

shown that surgical variables such as the number of vascular anastomoses and the use of a donor iliac artery interposition graft are the main risk factors for hepatic artery thrombosis.[22-24] Far fewer studies have focused on potential risk factors for central venous thromboembolic complications, and the pathogenesis of this type of thrombotic complication in liver transplantation remains largely unknown.[21]

In conclusion, we observed a higher incidence of hepatic artery thrombosis and venous thromboembolic events in aprotinin-treated patients; however, this did not reach statistical significance. Therefore, the current analysis did not provide evidence that the intraoperative use of aprotinin is associated with an increased risk of postoperative thromboembolic complications. In contrast to recent studies in cardiac patients, we also found no evidence that the use of aprotinin is associated with a higher risk of postoperative mortality after liver transplantation.

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