

Reduced Need for Vasopressors in Patients Receiving Aprotinin during Orthotopic Liver Transplantation

I. Quintus Molenaar, M.D., Bruno Begliomini, M.D.,† Gerardo Martinelli, M.D.,‡ Hein Putter, Ph.D.,§ Onno T. Terpstra, M.D., Ph.D.,‖ Robert J. Porte, M.D., Ph.D.#*

Background: **Graft reperfusion in orthotopic liver transplantation is often associated with significant hemodynamic changes, including decreased systemic vascular resistance and arterial blood pressure. Vasopressive drugs are often required to maintain adequate perfusion pressure during the early postreperfusion period. The exact mechanism of this postreperfusion syndrome is unknown, but release of bradykinin, a potent vasodilatator, *via* the kallikrein system may play a role. Aprotinin is a broad-spectrum inhibitor of serine proteases such as kallikrein and therefore may ameliorate the postreperfusion syndrome and reduce the need for vasopressors.**

Methods: **In a randomized, double-blind study, the authors compared hemodynamic variables (systemic vascular resistance, cardiac index, arterial blood pressure, mean pulmonary artery pressure, central venous pressure) and the requirement of epinephrine during transplantation in 67 patients who received either high-dose aprotinin (2×10^6 kallikrein inhibitor units [KIU] at induction, continuous infusion of 1×10^6 KIU/h, 1×10^6 KIU before reperfusion; n = 24), regular-dose aprotinin (2×10^6 KIU at induction, continuous infusion of 0.5×10^6 KIU/h; n = 21), or placebo (n = 22).**

Results: **Baseline characteristics were similar for all three groups. Erythrocyte transfusion requirement was significantly higher in the placebo group compared with both aprotinin-treated groups. No major differences in hemodynamic variables were found between the three groups. The total amount of epinephrine (median, range) used during transplantation, however, was significantly lower in patients who received aprotinin (high dose, 20, 0–170 μg; regular dose, 30, 0–140 μg), compared with patients who received placebo (70, 0–2,970 μg; $P = 0.0017$). This difference was largely attributable to differences in the early postreperfusion period.**

Conclusions: **Prophylactic use of aprotinin ameliorates the postreperfusion syndrome in orthotopic liver transplantation, as reflected by a significant reduction in vasopressor requirements.**

GRAFT reperfusion in orthotopic liver transplantation (OLT) is frequently characterized by significant hemodynamic changes, including decreased systemic vascular resistance (SVR) and mean arterial blood pressure (MAP), and increased cardiac output and mean pulmonary artery pressure.[1–4] Vasopressive drugs are often required to maintain an adequate perfusion pressure during this period. The exact mechanisms underlying this "postreperfusion syndrome" are poorly understood, but activation of proteolytic cascades, like the kallikrein-kinin system, have been suggested to play a role.[1,2] Activated kallikrein digests high molecular weight kininogen by which bradykinin is released.[5] Bradykinin is a very potent vasodilatator and may be responsible for the acute hemodynamic disturbances after graft reperfusion.[3,6]

Aprotinin is a broad-spectrum antiserine protease and an inhibitor of several naturally occurring serine proteases such as plasmin, trypsin, and kallikrein.[7] There is a vast amount of experience with the use of aprotinin in cardiac surgery. In several prospective studies, aprotinin was convincingly shown to reduce blood loss and to ameliorate the systemic inflammatory response to the cardiopulmonary bypass system.[8–10] There is accumulating evidence that aprotinin exerts its effect by inhibiting proteolytic cascades like the plasmin and kallikrein systems. Based on these experiences in cardiac surgery, it has been suggested that aprotinin can be useful in OLT as well.[11,12]

In a randomized, double-blind, placebo-controlled study, we recently demonstrated that the use of aprotinin in OLT is associated with a significant reduction in intraoperative blood loss and transfusion requirements.[13] Based on its antiinflammatory and antikallikrein activity, we hypothesized that aprotinin may also ameliorate the postreperfusion syndrome during OLT, resulting in less hemodynamic instability and a reduced requirement of vasopressive drugs after graft reperfusion.

The aim of the present study was to compare hemodynamic variables and intraoperative need for vasopressors in patients who were enrolled in a randomized, placebo-controlled study on aprotinin in OLT.

Materials and Methods

Patients and Study Protocol

Sixty-seven patients, who underwent liver transplantation in one of the participating centers of the larger European Multicenter Study on the use of Aprotinin in Liver Transplantation, were included in this study. Exclusion criteria for this study were pediatric patients (age < 18 yr), patients with a history of thromboembolic disorders or malignancies, patients with previous exposure to aprotinin, and patients with previous liver transplantation. The local ethical committee (Commissione per la sperimetazione terapeutica ospedaliera del Poli-

* Resident, Department of Surgery, § Statistician, Department of Medical Statistics, ‖ Professor and Head, Department of Surgery, Leiden University Medical Center. † Anesthesiologist, ‡ Professor and Head, Department of Anesthesiology and Intensive Care, S. Orsola Hospital, Bologna, Italy. # Surgeon, Department of Surgery, University Hospital Groningen, Groningen, The Netherlands.

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Address reprint requests to Dr. Porte: Department of Surgery, University Hospital Groningen, P.O. Box 30.001, 9700 RB Groningen, The Netherlands. Address electronic mail to: r.j.porte@chir.azg.nl.

clinico S. Orsola-Malpighi, Bologna, Italy) approved the study protocol, and written informed consent was obtained for each patient. Patients were randomized into three different groups: high-dose aprotinin (n = 24), regular-dose aprotinin (n = 21), or placebo (n = 22). Patients in the high-dose group received a loading dose of 2×10^6 kallikrein inhibitor units [KIU] aprotinin (Trasylol; Bayer AG, Leverkusen, Germany) during induction of anesthesia, followed by a continuous infusion of 1×10^6 KIU per hour and an additional 1×10^6 KIU 30 min before reperfusion. The regular-dose group received a loading dose of 2×10^6 KIU aprotinin, followed by 0.5×10^6 KIU aprotinin per hour. The placebo group received identical volumes of a 0.9% sodium chloride solution, provided in identical bottles. In all three study groups, infusion of study medication was discontinued 2 h after graft reperfusion. The study medication was randomized by the manufacturer in blocks of 12 case packs (four patients in each group). Case packs were identifiable by a randomization number only.

Aprotinin plasma concentrations were measured at five time points in a subset of 38 patients, using an enzyme-linked immunoabsorbent assay (Courtesy of Dr G. Lemm; Bayer AG, Wuppertal, Germany).

Surgical Procedure

Liver transplantation was either performed with preservation of the recipient's inferior vena cava during hepatectomy without using veno-venous bypass ("piggyback" technique) or with resection of the recipient's retrohepatic inferior vena cava with veno-venous bypass (conventional technique). Before reperfusion, liver grafts were flushed with 600 ml albumin, 5% solution, *via* the portal vein. No patient received intraoperative heparin. For description purpose, liver transplantation is divided into three stages: preanhepatic, anhepatic, and postreperfusion period.

Anesthesia and Hemodynamic Monitoring

Three anesthesiologists were involved in the study, each performing approximately one third of the procedures. Anesthesia was induced with thiopental, fentanyl, vecuronium, and oxygen and was maintained with isoflurane, fentanyl, vecuronium, and an oxygen and air mixture (fractional inspired oxygen pressure, 0.5). Blood product requirements were recorded for each stage of the operation. These data have been previously published as part of the larger multicenter study (European Multicenter Study on the use of Aprotinin in Liver Transplantation).[13]

Measured hemodynamic variables were cardiac output, SVR, MAP, mean pulmonary arterial pressure, and central venous pressure. Systemic vascular resistance index (SVRI) and cardiac index (CI) were calculated using standard formulas. Hemodynamic variables were determined by a Swan-Ganz pulmonary catheter (IntelliCath; Baxter-Edwards, Irvine, CA) connected to a Vigilance Baxter monitor (Baxter-Edwards). Pulmonary artery, central venous, and systemic arterial (radial) pressures were displayed on a Hewlett Packard M1166A Component Monitoring System, Model 68S (Hewlett-Packard, Palo Alto, CA).

Hemodynamic variables were determined at six standardized time points during transplantation: after induction of anesthesia, 10 min before the end of the preanhepatic period, 10 min before the end of the anhepatic period, and 5, 30, and 120 min after reperfusion. Besides hemodynamic monitoring, hemoglobin levels were measured at the same intraoperative time points. Perioperative hemoglobin change was calculated for all three groups.

Use of Vasopressive Drugs

According to local protocol, all patients received a continuous infusion of dopamine 3 $\mu g \cdot kg^{-1} \cdot min^{-}$ during the entire operation. Epinephrine was administered according to standardized guidelines. Boluses of 10 μg were given whenever systolic blood pressure fell to less than 70 mmHg, despite adequate infusion of fluids, or when a sudden decrease in arterial pressure of more than 30% occurred in the absence of increased bleeding.

Statistical Analysis

Statistical analysis was performed using SPSS 9.0 (SPSS Inc., Chicago, IL) and SAS 6.12 (SAS Institute Inc., Cary, NC) for Windows (Microsoft Corp., Redmond, WA). Transplant variables, transfusion requirements, and need for epinephrine were nonparametrically distributed and expressed as median. Comparisons among the three groups were made using the Kruskall–Wallis test or the chi-square test.

Two-way analysis of variance with repeated measures was used to analyze the hemodynamic variables over time. Where necessary, variables were log-transformed to ensure normality. Generalized least-squares means of the fixed effects were used as estimators of the means of the variables, expected for a complete balanced design. Bonferroni adjustment of *P* values was used in testing differences of mean values postreperfusion with values at the end of the anhepatic period.

Results

Patient and Transplant-related Variables

Patient characteristics and transplantation data are presented in table 1. The three groups were comparable for sex, weight, height, cause of liver disease, severity of liver disease, cold ischemia time, duration of operation, or surgical technique. Although median age in the high-dose group was slightly higher, there was no difference between the regular-dose and the placebo group.

Table 1. Patient Characteristics and Transplant Variables

Variable	HD Aprotinin (n = 24)	RD Aprotinin (n = 21)	Placebo (n = 22)	*P* Value*
Age (yr)				
Median	56	48	47	0.03
Range	(18–63)	(18–62)	(19–61)	
Weight (kg)				
Median	71	74	76	0.17
Range	(54–93)	(51–92)	(54–110)	
Height (cm)				
Median	170	171	170	0.44
Range	(154–188)	(165–183)	(157–190)	
Male/female	18/6	18/3	21/1	0.15
Diagnosis				
Postnecrotic cirrhosis	16	19	19	0.08
Biliary cirrhosis	3	0	0	
Miscellaneous†	5	2	3	
Child–Pugh classification				
A	1	3	2	0.83
B	12	10	11	
C	11	8	9	
Piggyback (Y/N)	20/4	17/4	13/9	0.12
Cold ischemia period (min)				
Median	540	504	534	0.79
Range	(345–726)	(327–770)	(300–780)	

* Kruskall–Wallis or chi-square test. † High dose (HD): acute hepatic failure 1, autoimmune hepatitis 1, Criggler–Najar 1, hepatic fibrosis 1, Wilson 1; regular dose (RD): acute hepatic failure 2; placebo: acute hepatic failure 2, amyloidosis 1.

Intraoperative aprotinin plasma levels varied between 100 and 150 KIU/ml in the regular-dose group, whereas they were more than 200 KIU/ml in patients receiving high-dose aprotinin, except for the first sample taken immediately after induction of anesthesia (175 KIU/ml).

Total erythrocyte requirement (homologous and autologous) was significantly lower in both high- and regular-dose groups compared with placebo ($P = 0.001$). Median (interquartile range) erythrocyte requirement in the placebo group was 2,675 ml (1,488–5,753 ml), whereas 1,025 ml (600–1,744 ml) and 1,135 ml (150–2,075 ml) were required in the high- and regular-dose groups, respectively. The amount of fresh frozen plasma transfused during transplantation was also significantly lower in the aprotinin treated groups (high-dose group, 1,875, 1,000–2,475 ml; regular-dose group, 1,700, 1,150–2,250 ml) compared with placebo (3,275, 1,725–4,788 ml; $P = 0.009$). No significant differences were observed between the high- and regular-dose groups.

Intraoperative levels of hemoglobin followed a relatively stable course in each group, and no significant differences were observed between the three groups during transplantation. Median (range) levels of hemoglobin at 5 min after graft reperfusion were 9.6 (7.6–11.5), 10.2 (8.5–14.4), and 9.3 mg/dl (5.7–11.5) in the high-dose, regular-dose, and placebo groups, respectively ($P = 0.08$). Perioperative hemoglobin change was −0.80 (−3.3 to +2.5), −1.0 (−3.1 to +1.4), and −1.7 mg/dl (−5.5 to + 1.9), respectively ($P = 0.41$).

Hemodynamic Variables

Hemodynamic variables of the systemic and pulmonary circulation are presented in table 2. Except for small, but significant, differences in MAP shortly after graft reperfusion, no major differences in hemodynamic variables were found between the three groups. A significant decrease in MAP was seen after graft reperfusion in all three groups. At 5 min after reperfusion, however, this drop in MAP was significantly lower in the placebo group, compared with the regular dose group. At 2 h after reperfusion, MAP restored toward prereperfusion values in all three groups.

A significant increase in CI as well as decrease in SVR was observed in all three groups in the early postreperfusion period, but no significant differences were seen between the groups. Mean pulmonary artery pressure gradually increased after graft reperfusion without differences between the groups.

Use of Vasopressive Drugs

Table 3 presents the amount of epinephrine required during each stage of the operation. The total amount of epinephrine was significantly lower in the high- and regular-dose aprotinin groups, compared with the placebo group. Analysis per stage of the operation showed that this difference was largely attributable to the lower epinephrine requirements in the aprotinin-treated patients during the early postreperfusion period. The number of patients requiring epinephrine during OLT was

Table 2. Hemodynamic Variables During Orthotopic Liver Transplantation

	High-dose Aprotinin (n = 24)		Regular-dose Aprotinin (n = 21)		Placebo (n = 22)		
	Mean	95% CI	Mean	95% CI	Mean	95% CI	*P* Value
MAP (mmHg)							
After induction	73.8	68.6–78.9	74.5	69.0–79.9	67.7	62.4–73.1	0.16
End preanhepatic period	72.4	67.2–77.6	76.7	71.2–82.1	68.7	63.4–74.1	0.12
End anhepatic period	71.8	66.6–77.0	73.1	67.5–78.6	67.7	62.2–73.1	0.35
5 min after reperfusion	59.5*	54.1–64.9	70.8	65.2–76.3	58.4*	52.8–64.0	0.003
30 min after reperfusion	65.2	60.0–70.3	65.8	60.3–71.2	58.9*	53.5–64.2	0.14
120 min after reperfusion	70.9	65.7–76.2	72.7	67.3–78.2	70.8	65.4–76.1	0.85
Cardiac index ($l \cdot min^{-1} \cdot m^{-2}$)							
After induction	4.04	3.57–4.58	4.43	3.89–5.06	4.17	3.66–4.75	0.60
End preanhepatic period	4.13	3.65–4.67	4.74	4.15–5.40	3.70	3.25–4.21	0.03
End anhepatic period	3.95	3.49–4.47	3.61	3.15–4.13	3.74	3.29–4.26	0.61
5 min after reperfusion	4.39	3.86–4.99	5.01*	4.39–5.72	4.19	3.68–4.78	0.15
30 min after reperfusion	5.27*	4.65–5.96	5.27*	4.62–6.01	4.70*	4.13–5.34	0.36
120 min after reperfusion	4.72*	4.17–5.35	5.43*	4.76–6.19	4.61*	4.06–5.24	0.17
SVRI ($dyn \cdot cm^{-5} \cdot min^{-1} \cdot m^{-2}$)							
After induction	1,283	1,099–1,498	1,177	998–1,387	1,138	969–1,336	0.55
End preanhepatic period	1,260	1,079–1,472	1,168	991–1,377	1,306	1,112–1,533	0.62
End anhepatic period	1,271	1,088–1,484	1,432	1,213–1,691	1,274	1,083–1,498	0.51
5 min after reperfusion	873*	744–1,025	948*	803–1,119	937*	794–1,106	0.75
30 min after reperfusion	842*	721–984	853*	724–1,005	860*	733–1,010	0.98
120 min after reperfusion	1,023*	875–1,197	907*	770–1,069	1,047*	891–1,232	0.42
MPAP (mmHg)							
After induction	16.3	14.3–18.6	17.1	14.9–19.6	14.7	12.9–16.8	0.28
End preanhepatic period	13.3	11.7–15.2	14.3	12.5–16.4	12.9	11.3–14.7	0.55
End anhepatic period	15.5	13.6–17.6	12.5	10.8–14.3	13.0	11.4–14.9	0.05
5 min after reperfusion	15.7	13.7–18.0	18.1*	15.7–20.7	16.0*	14.0–18.4	0.32
30 min after reperfusion	18.6	16.4–21.2	16.8*	14.7–19.3	14.7	12.8–16.8	0.04
120 min after reperfusion	18.0	15.8–20.5	19.1*	16.7–21.9	16.9*	14.8–19.3	0.45
CVP (mmHg)							
After induction	7.18	5.65–8.72	8.05	6.42–9.68	7.50	5.91–9.09	0.75
End preanhepatic period	6.40	4.86–7.94	6.76	5.13–8.39	6.27	4.68–7.86	0.91
End anhepatic period	7.57	6.04–9.11	7.40	5.75–9.04	6.97	5.36–8.58	0.86
5 min after reperfusion	8.43	6.85–10.0	9.11	7.46–10.8	7.79	6.14–9.43	0.54
30 min after reperfusion	8.68	7.14–10.2	8.81	7.18–10.4	7.64	6.04–9.23	0.53
120 min after reperfusion	9.17	7.62–10.7	10.2*	8.56–11.8	8.14	6.53–9.75	0.21

* $P < 0.05$ with Bonferroni adjustment compared with values before reperfusion (end anhepatic period).

CI = confidence interval; MAP = mean arterial pressure; SVRI = systemic vascular resistance index; MPAP = mean pulmonary artery pressure; CVP = central venous pressure.

also significantly lower in the high- (16/24, 66%) and regular-dose (15/21, 71%) groups, compared with the placebo group (21/22, 95%; $P = 0.046$).

Discussion

Graft reperfusion in OLT is often associated with hemodynamic instability requiring infusion of fluids and the administration of vasopressive drugs.[14,15] Hemodynamic changes during the early postreperfusion period are characterized by a combination of reduced MAP and SVRI and increased CI and mean pulmonary artery pressure, and this has been referred to as the postreperfusion syndrome.[1,2,4,16] In accordance with previous studies,[2,4,16,17] we observed a significant decrease in MAP and SVRI at 5 and 30 min after reperfusion, compared with prereperfusion values (end of anhepatic period). The principle finding of the current study was that prophylactic administration of aprotinin reduced the need for vasopressors during OLT, especially during the early postreperfusion period. The total amount of epinephrine used during transplantation was significantly lower in patients who received aprotinin, compared with those who received placebo. Analysis per stage of the operation demonstrated that this difference was mainly caused by a reduction in epinephrine requirements during the first 30 min after graft reperfusion. No significant differences in any of the hemodynamic variables were observed between the three groups, except for a significantly higher MAP in the regular-dose group at 5 min after reperfusion. Recently, Milroy *et al.*[2] have reported similar effects of aprotinin on the hemodynamic profile during OLT. In a placebo-controlled, double-blind study, these authors found significantly more changes in SVRI and CI postreperfusion in patients who received placebo, compared with aprotinin-treated patients. In con-

Table 3. Epinephrine during Transplantation

Total Amount of Epinephrine (μg)	HD Aprotinin (n = 24)	RD Aprotinin (n = 21)	Placebo (n = 22)	*P* Value*
Before reperfusion				
Median	0	0	0	0.07
Range	(0–20)	(0–110)	(0–1,190)	
0–30 min after reperfusion				
Median	20	20	70	0.0007
Range	(0–140)	(0–130)	(0–600)	
30–60 min after reperfusion				
Median	0	0	0	0.05
Range	0	(0–40)	(0–100)	
60 min after reperfusion–end				
Median	0	0	0	0.67
Range	(0–50)	(0–20)	(0–2,100)	
Entire surgery				
Median	20	30	70	0.0017
Range	(0–170)	(0–140)	(0–2,970)	

* Kruskall–Wallis test.

HD = high-dose; RD = regular-dose.

trast with our findings, these investigators, however, did not observe a difference in the number of patients who required vasopressive drugs among the two groups. The more aggressive treatment of hemodynamic changes with epinephrine in our study may explain why we observed no differences in SVRI and CI, but yet found a significant difference in the use of epinephrine, whereas Milroy *et al.*[2] observed significant differences in hemodynamic variables, but not in the use of vasopressors. Both our study and the one performed by Milroy *et al.*[2] provide evidence that aprotinin improves hemodynamic stability during the reperfusion period in OLT.

The hemodynamic effect of aprotinin may be explained by its antikallikrein activity. Others have shown that graft reperfusion in OLT is associated with activation of the contact system leading to kallikrein formation.[3,18] Kallikrein digests high–molecular-weight kininogen, which leads to the release of the very potent vasodilator bradykinin, resulting in decreased MAP and SVRI.[2,3,19] Although *in vitro* studies have indicated that aprotinin concentrations more than 200 KIU/ml are required for adequate inhibition of kallikrein, our results suggest that *in vivo*, this effect can already be achieved at lower aprotinin plasma concentrations of approximately 100 KIU/ml. We obtained aprotinin plasma concentrations of approximately 100 KIU/ml in the regular-dose group and 200 KIU/ml in the high-dose group, and no differences were found between the two groups with respect to vasopressor requirements. This finding is in accordance with the results of Milroy *et al.*,[2] who also found an effect on hemodynamics at concentrations of approximately 100 KIU/ml. Possibly, the presence of naturally occurring inhibitors *in vivo* contributes to the antikallikrein effect of aprotinin, and this may explain the difference between *in vitro* and *in vivo* studies.

Other mechanisms thought to play a role in the origin of the postreperfusion syndrome are a sudden increase in venous return, cardiac reflexes, and release of substances from the graft, such as proinflammatory cytokines.[20] Studies in patients undergoing cardiac surgery have demonstrated that aprotinin ameliorates the systemic inflammatory response and the release of proinflammatory cytokines secondary to the cardiopulmonary bypass system.[9] It was not our aim to study the mechanisms by which aprotinin ameliorates the postreperfusion syndrome during OLT, and whether inhibition of kallikrein or cytokine release is more important cannot be deducted from this study. Evidence that aprotinin improves hemodynamic stability by inhibition of kallikrein could come from the measurement of kallikrein–aprotinin complexes in the circulation. This would require the development of a specific assay for quantification of these complexes.

The main objective of using aprotinin during OLT is to reduce transfusion requirements and hyperfibrinolysis by virtue of its antiplasmin activity. We have recently shown that the use of aprotinin significantly reduces blood loss and transfusion requirements during OLT by approximately 50% and 30%, respectively.[13] The current study indicates that an additional beneficial effect of aprotinin is a reduction in the requirement of vasopressive drugs, especially after graft reperfusion.

We have reason to believe that this difference in vasopressor requirement between placebo- and aprotinin-treated patients is not simply the result of inadequate replacement of higher blood loss in the placebo group. First, there was no difference in perioperative hemoglobin levels among the three groups, which indicates that blood loss was adequately and equally corrected by the transfusion of blood products (erythrocytes and fresh frozen plasma) in all three groups. Second, no significant differences were found in central venous pressure between the three groups, which indicates that intravascu-

lar filling status of patients who received placebo was not lower than of those who received aprotinin.

In conclusion, our results confirm previous observations that OLT is associated with a postreperfusion syndrome, characterized by a decrease in MAP and SVRI and an increase in CI and mean pulmonary artery pressure. The novelty of this study is that the prophylactic use of aprotinin during transplantation significantly reduces the need for vasopressive drugs to maintain hemodynamic stability. This effect of aprotinin can be seen at plasma concentrations of approximately 100 KIU/ml, which are obtained with the regular-dose scheme. In combination with the observed reduction in blood loss and transfusion requirements,[13] these findings give additional support for the prophylactic use of aprotinin in patients undergoing OLT who have no contraindications. Because our previous study has not shown a statistically significant difference in blood loss and transfusion requirements between the high-dose and the regular-dose groups, we favor the regular dose in these patients.

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