Fibrinolysis During Liver Transplantation Is Enhanced by Using Solvent/Detergent Virus-Inactivated Plasma (ESDEP®)

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After the introduction of solvent/detergent-treated plasma (ESDEP®) in our hospital, an increased incidence of hyperfibrinolysis was observed (75% vs 29%; $P = 0.005$) compared with the use of fresh frozen plasma for liver transplantation. To clarify this increased incidence, intraoperative plasma samples of patients treated with fresh frozen plasma or ESDEP were analyzed in a retrospective observational study. During the anhepatic phase, plasma levels of D-dimer (6.58 vs 1.53 μg/mL; $P = 0.02$) and fibrinogen degradation products (60 vs 23 mg/L; $P = 0.018$) were significantly higher in patients treated with ESDEP. After reperfusion, differences increased to 23.5 vs 4.7 μg/mL (D-dimer, $P = 0.002$) and 161 vs 57 mg/L (fibrinogen degradation products, $P = 0.001$). The amount of plasma received per packed red blood cell concentrate, clotting tests, and levels of individual clotting factors did not show significant differences between the groups. α_2-Antiplasmin levels, however, were significantly lower in patients receiving ESDEP during the anhepatic phase (0.37 vs 0.65 IU/mL; $P < 0.001$) and after reperfusion (0.27 vs 0.58 IU/mL; $P = 0.001$). Analysis of α_2-antiplasmin levels in ESDEP alone showed a reduction to 0.28 IU/mL (normal >0.95 IU/mL) because of the solvent/detergent process. Therapeutic consequences for the use of ESDEP in orthotopic liver transplantation are discussed in view of an increased incidence of hyperfibrinolysis caused by reduced levels of α_2-antiplasmin in the solvent/detergent-treated plasma.
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To minimize the risk of transmission of the lipid-coated viruses hepatitis B virus, hepatitis C virus, and human immunodeficiency virus in blood component substitution therapy, solvent/detergent (SD)-treated plasma has been used in our hospital since 1996. Since its introduction, an increase in hyperfibrinolysis during orthotopic liver transplantation (OLT) has been observed. Enhanced fibrinolytic activity during OLT has been attributed to high levels of tissue-type plasminogen activator (t-PA) (1,2) and contributes to serious bleeding complications (3). Plasma levels of t-PA peak just after reperfusion as a result of the absent clearance during the anhepatic phase and the release of t-PA from damaged endothelial cells in the donor liver (4). *In vitro* studies demonstrated some alterations in individual clotting factors caused by SD treatment, particularly a loss of clotting factor VIII (up to 20%), protein S (35%), and α_2-antiplasmin (up to 76%) (5,6). In this observational study, intraoperative plasma samples of patients treated with SD-treated plasma or fresh-frozen plasma (FFP) were analyzed to find an explanation for the increased incidence of hyperfibrinolysis observed with the use of SD-treated plasma (ESDEP®; CLB Amsterdam, The Netherlands) during OLT.

Methods

All the studies, including this study, running in the Rotterdam liver transplantation center are under the surveillance of the medical ethics committee of the Erasmus University Rotterdam. From June 1994 to March 1997, 67 patients underwent OLT for end-stage cirrhosis after written, informed consent was obtained. In 41 patients, complete coagulation follow-up during the procedure was present. From June 1994 to December 1995, clotting factors were substituted in 21 patients with FFP (300 mL; CLB Amsterdam). After January 1996, SD virus-inactivated plasma (ESDEP, 200 mL) was used in 20 patients. The ESDEP was prepared from pooled plasma of 2000 voluntary Dutch blood donors, and virus inactivation was realized by treating the pooled plasma with

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1% tri-(*n*-butyl)phosphate and 1% Triton X-100 (7) by Octapharma (Octapharma, Vienna, Austria). Anesthesia was induced with Thiopental 3–4 mg/kg, midazolam 0.1 mg/kg, and sufentanil 0.5 μg/kg. Muscle relaxation was achieved with pancuronium 0.1 mg/kg. Anesthesia was maintained with midazolam 0.1 $mg \cdot kg^{-1} \cdot h^{-1}$, sufentanil 0.2 $\mu g \cdot kg^{-1} \cdot h^{-1}$, and pancuronium 25 μg/kg. Calcium chloride was given by infusion as required. Inotropic support was provided if necessary with dopamine 5–10 $\mu g \cdot kg^{-1} \cdot min^{-1}$ and, sometimes, epinephrine 0.25 $\mu g \cdot kg^{-1} \cdot min^{-1}$. Packed red blood cells (PRBC) were transfused to maintain a hematocrit of 25%. FFP or ESDEP was infused 10 mL/kg in the preanhepatic phase to correct severe coagulopathy and was then infused in a ratio of 1 mL/mL PRBC or per milliliter of salvaged blood. Platelet count was kept $>80 \times 10^9$/L by infusion of platelet suspension. If fibrinogen decreased to <1.0 g/L, purified fibrinogen (Hemocomplettan P; CLB Amsterdam) was given. A venovenous bypass with heparin-coated tubing (Bioconsole; Biomedicus, Minneapolis, MN) was used after trial clamping of the caval vein. A blood cell salvage system (CATS; Fresenius, Schweinfurt, Germany) and rapid infusion system (Haemonetics, Braintree, MA) were routinely used.

Routine coagulation tests (activated partial thromboplastin time, partial thromboplastin time, thrombocyte count, thrombin time 5E and 10E, fibrinogen, Thrombotest™, and Normotest™) were performed on arterial blood collected 5 min after the induction of anesthesia (but before the administration of plasma), 5 min after hepatectomy, 5 min after reperfusion of the donor liver, and at the end of the procedure. Fibrinolysis was detected with four-channel Thrombelastograph (TEG®; Haemoscope Corp., Skokie, IL) recordings according to the criteria of Kang et al. (8), standard at sampling times and further when clinically indicated. The following values were measured: reaction time, coagulation time, maximal amplitude (MA), and clot lysis index (CLI) at 30 and 60 min ($MA - MA_t)/MA \times 100\%$. Tranexamic acid (500–1000 mg) was administered when TEG® recordings showed a CLI_{60} of more than 10% and generalized oozing occurred. After the administration of tranexamic acid, the result was evaluated with a new TEG® recording, and, if necessary, the treatment was repeated with dosages of 10–15 $mg \cdot kg^{-1} \cdot h^{-1}$. To confirm the diagnosis of fibrinolysis, D-dimers were analyzed afterward in stored plasma by using the Miniquant automated agglutination analyzer and Miniquant test kit (Biopool Kordia, Leiden, The Netherlands). Fibrinogen degradation products (FDP) were also analyzed in stored plasma by using a Latex agglutination reaction (Diagnostica Stago Roche, The Netherlands). Clotting factor II, VII, VIII, IX, and X levels were analyzed afterward by standard clotting assays in stored plasma (−80°C) on an automatic coagulation laboratory (Instrumentation Laboratory, Breda, The Netherlands) by using human deficient plasma (Biopool Kordia). Antithrombin-III and α_2-antiplasmin were determined with a chromogenic assay (Dade-Behring, Leusden, The Netherlands). All data are presented as mean ± SEM. After normality was tested with Shapiro-Wilk statistics, a Student's *t*-test or Mann-Whitney *U*-test was used for data analysis. α_2-Antiplasmin levels had logarithmic transformation before analysis, and the changes from baseline α_2-antiplasmin levels were investigated with repeated-measures analysis of variance including time period and type of plasma as covariates. For 2×2 table data, the χ^2 test with the Yates correction or Fisher's exact test was used. Differences were considered significant for $P < 0.05$.

Results

The characteristics of the FFP- and ESDEP-Treated groups are summarized in Table 1. In patients treated with FFP ($n = 21$), hyperfibrinolysis was seen in six individuals (29%): in one patient during the preanhepatic phase, in one patient during both the preanhepatic and the anhepatic phase, in one patient during both the anhepatic and reperfusion phase, and in three patients after reperfusion. In the ESDEP-Treated group ($n = 20$), hyperfibrinolysis was present in 15 patients (75% vs 29%; $P = 0.005$). In 4 patients, an episode of hyperfibrinolysis occurred during the preanhepatic phase (20% vs 10%; not significant); in 8 patients, during the anhepatic phase (40% vs 10%; $P = 0.03$); and in 10 patients, after reperfusion (50% vs 19%; $P = 0.05$). In 7 of these 15 patients with hyperfibrinolysis, it occurred repeatedly: in 3 patients during both the preanhepatic and the anhepatic phase and in 4 patients in the anhepatic phase and after reperfusion. CLIs after 60 min were 4% vs 26% ($P = 0.03$) in the anhepatic phase and 4% vs 40% ($P = 0.03$) after reperfusion (Table 2). The dose of tranexamic acid given in both groups to patients with excessive fibrinolysis was similar. In the patients treated with FFP, 6500 mg of tranexamic acid was administered to six patients (29%) (mean dose, 1083 mg per patient). In the ESDEP-Treated group, 12 patients (60%) received 15,250 mg of tranexamic acid (mean dose, 1271 mg per patient; not significant).

Analysis of standard coagulation variables during the procedure revealed no significant differences between patients treated with FFP or ESDEP, except for factor VIII after induction and the prothrombin time in the anhepatic phase (Table 3). However, D-dimer and FDP levels were significantly higher in the ESDEP-treated patients in the anhepatic phase and after reperfusion, consistent with the increased fibrinolytic activity recorded on TEG® (Table 3).

Table 1. Basic Characteristics of Patients Undergoing Orthotopic Liver Transplantation

Variable	FFP (n = 21)	ESDEP (n = 20)
Age (yr)	53 (23–65)*	44 (23–62)
Male/female	9/12	15/5
Indication (n)		
Viral hepatitis cirrhosis	6	6
Cholestatic liver disease	10	8
Other cirrhosis	5	6
Operation time (min)	419 (14)	436 (21)
Blood loss (mL)	12,173 (1,907)	15,191 (3,155)
Transfusions		
PRBC (U)	13.1 (1.8)	15.3 (2.9)
Cell salvage blood (mL)	2,481 (655)	2,655 (981)
Plasma (mL)	4,271 (616)	5,440 (903)
Fibrinogen (g)	4.7 (0.8)	7.2 (1.6)
Platelets (U)	19.5 (2.4)	20.0 (3.6)
Plasma/PRBC (mL)	342 (30)	383 (26)

Values are mean (SEM) or (range).
FFP = fresh frozen plasma; ESDEP® = solvent/detergent-treated plasma; PRBC = packed red blood cells.
* $P < 0.05$ versus ESDEP®.

Also, determination of α_2-antiplasmin levels showed significant differences between treatment with FFP or ESDEP (Fig. 1). α_2-Antiplasmin levels after the onset of anesthesia were not statistically different in the FFP- and the ESDEP-Treated groups. In patients who received FFP, α_2-antiplasmin levels remained relatively stable and decreased from 0.76 to 0.65 IU/mL in the anhepatic phase, decreased to 0.58 IU/mL after reperfusion, and leveled out at 0.58 IU/mL at the end of the procedure. The corresponding levels in patients treated with ESDEP were 0.64 IU/mL (not significant), 0.37 IU/mL ($P < 0.001$), 0.27 IU/mL ($P = 0.006$), and 0.40 IU/mL ($P = 0.03$), respectively. Repeated analysis of variance confirmed that type of plasma was responsible for the decrease from baseline value, independent from the time course. Analysis of ESDEP itself revealed normal levels of all clotting factors (>0.81 IU/mL), AT-III (>0.81 IU/mL), protein C (0.80 IU/mL), and plasminogen (0.94 IU/mL). Levels of factor VIII (0.71 IU/mL) and protein S (0.58 IU/mL) were slightly decreased, but levels of α_2-antiplasmin were severely decreased to 0.28 ± 0.02 IU/mL (normal, 0.95–1.20 IU/mL) (5). Linear regression showed statistically significant relationships between the level of α_2-antiplasmin and the CLI_{60} ($P < 0.01$) and CLI_{60} ($P < 0.01$), the level of FDP and CLI_{30} ($P < 0.03$), and the D-dimer level and CLI_{60} ($P < 0.01$) and CLI_{60} ($P < 0.01$). Despite the increased fibrinolysis, there was no difference in total blood loss between patients receiving FFP or ESDEP, but blood loss was significantly larger in the 21 of 41 patients from both groups in whom hyperfibrinolysis occurred (18,054 ± 2,469 mL vs 8,683 ± 1,339 mL; $P < 0.001$). In addition, the transfusion requirements for PRBC, platelets, fibrinogen, and plasma were also larger in patients with hyperfibrinolysis (all $P < 0.001$).

Discussion

OLT has become the standard treatment for end-stage liver disease, but the procedure still can be associated with severe disorders of hemostasis (9). A key role in the pathogenesis of intraoperative bleeding is played by enhanced fibrinolysis during the anhepatic and reperfusion phase (10,11). To minimize the risk of viral transmission, SD virus-inactivated plasma was introduced in 1996 in our hospital, and thereafter an increase in hyperfibrinolysis in patients undergoing OLT was observed. SD treatment of FFP is an effective method to reduce lipid-coated viruses by >5 log 10 (12,13), but it has been reported that because of the SD process, the concentration of factor VIII, protein S, and α_2-antiplasmin is reduced (5,6).

α_2-Antiplasmin is a main physiological inhibitor of t-PA-induced fibrinolysis and fibrinogenolysis (14,15), which are held responsible for uncontrollable intraoperative bleeding. Inhibition of this fibrinolysis may occur at the level of plasminogen activation by plasminogen activator inhibitor or at the level of plasmin by α_2-antiplasmin (16). Once large amounts of t-PA are released into the circulation of the recipient, α_2-antiplasmin plays a key role in the scavenging of the formed free plasmin. Free plasmin is extremely rapidly inactivated by α_2-antiplasmin; the half-life of free plasmin is estimated to be approximately 0.1 seconds. Without adequate α_2-antiplasmin levels, a small amount of t-PA can start the offset of systemic fibrinolysis (17), because the fibrin degradation products can amplify the plasminogen activation (18).

Although the efficacy of SD plasma in clinical studies in patients with coagulation disorders has been established (19,20), the balance between pro- and antifibrinolytic activity in our patients seems to be disturbed during OLT by SD plasma substitution. In patients with chronic liver disease, enhanced fibrinolysis occurred approximately three times more in the anhepatic phase and after reperfusion in patients who received ESDEP than in patients treated with FFP. Determination of α_2-antiplasmin concentrations in ESDEP showed decreased levels, in accordance with the results presented in the literature (5,6). In 47% of the patients treated with ESDEP, hyperfibrinolytic episodes did recur, despite adequate treatment of the first hyperfibrinolytic episode, proven by normalization of the TEG® recordings. We think that this effect is caused by the large plasma exchanges in OLT, which dilute the level of α_2-antiplasmin in the patient to the level of ESDEP itself.

Table 2. Coagulation Analysis Variables During Orthotopic Liver Transplantation in Patients Treated with FFP and ESDEP

Variable	After induction		Anhepatic phase		After reperfusion	
	FFP	ESDEP	FFP	ESDEP	FFP	ESDEP
R (mm)	21.7 (0.6)	23.6 (2.7)	15.5 (1.6)	16.1 (2.5)	24.1 (1.0)	29.6 (3.9)
R + K (mm)	31.0 (0.9)	32.0 (3.0)	24.6 (2.1)	23.3 (3.3)	37.5 (1.8)	44.3 (5.0)
Ang (deg)	50.1 (4.7)	42.2 (3.1)	43.7 (4.1)	52.4 (3.6)	41.5 (4.2)	33.7 (3.5)
MA (mm)	47.7 (2.5)	54.5 (3.1)	40.8 (3.0)	48.0 (3.7)	32.2 (3.2)	35.0 (3.9)
CLI_{30} (%)	1.6 (0.4)	3.1 (2.1)	1.7 (0.5)*	16.8 (7.5)	2.0 (0.5)*	31.6 (9.9)
CLI_{60} (%)	4.3 (0.8)	7.2 (2.2)	3.9 (1.1)*	26.2 (9.6)	4.2 (1.0)*	39.7 (10.7)

Values are mean (SEM).
FFP = fresh frozen plasma; ESDEP® = solvent/detergent-treated plasma; R = R time; K = K time; Ang = angle; MA = maximum amplitude; CLI = clot lysis index at 30 and 60 min.
* $P < 0.05$ versus ESDEP.

Table 3. Coagulation Variables During Orthotopic Liver Transplantation

Variable	After induction		Anhepatic phase		After reperfusion	
	FFP	ESDEP	FFP	ESDEP	FFP	ESDEP
aPTT (s)	43 (3)	46 (3)	68 (13)	113 (19)	157 (18)	181 (19)
PT (s)	17.6 (1.7)	15.8 (0.9)	15.1 (0.5)*	24.0 (5.5)	17.4 (1.0)	24.0 (5.2)
Thrombin time 10E (s)	17 (1)	20 (2)	19 (2)	25 (4)	26 (4)	33 (6)
Platelets ($\times 10^9$/L)	108 (16)	113 (17)	89 (19)	75 (10)	90 (14)	79 (9)
Fibrinogen (g/L)	1.8 (0.1)	2.2 (0.3)	1.5 (0.1)	1.6 (0.2)	1.5 (0.1)	1.4 (0.2)
FII (IU/mL)	0.48 (0.05)	0.48 (0.05)	0.47 (0.03)	0.40 (0.04)	0.39 (0.02)	0.37 (0.03)
FVII (IU/mL)	0.43 (0.05)	0.45 (0.05)	0.41 (0.03)	0.37 (0.04)	0.34 (0.02)	0.35 (0.03)
FX (IU/mL)	0.56 (0.04)	0.55 (0.04)	0.49 (0.02)	0.44 (0.04)	0.39 (0.02)	0.38 (0.03)
FVIII (IU/mL)	2.17 (0.25)*	3.41 (0.52)	1.29 (0.21)	1.70 (0.30)	0.80 (0.12)	1.01 (0.24)
FIX (IU/mL)	0.51 (0.07)	0.58 (0.08)	0.36 (0.05)	0.36 (0.06)	0.22 (0.03)	0.19 (0.04)
D-dimer (μg/mL)	0.46 (0.14)	1.01 (0.40)	1.53 (0.37)*	6.58 (1.98)	4.70 (1.97)†	23.47 (6.56)
FDP (mg/L)	—	—	23 (5)†	60 (16)	57 (11)†	161 (24)

Values are mean (SEM).
FFP = fresh frozen plasma; ESDEP® = solvent/detergent-treated plasma; aPTT = activated partial thromboplastin time; PT = prothrombin time; FII, FVII, FX, FVII, FIX = clotting factors.
* $P < 0.05$ versus ESDEP; † $P < 0.01$ versus ESDEP.

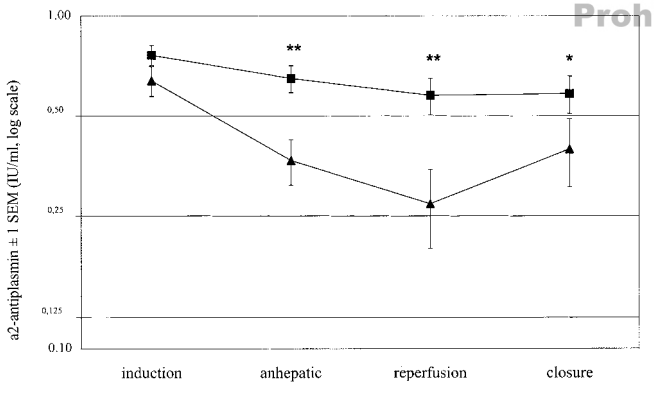

Figure 1. Intraoperative time course of the α_2-antiplasmin levels. ■Patients with chronic liver disease treated with fresh frozen plasma ($n = 21$). ▲ Patients with chronic liver disease treated with solvent/detergent virus-inactivated plasma ($n = 20$). *$P < 0.05$; **$P < 0.01$.

In a randomized multicenter study by Freeman et al. (21), no differences were seen in coagulation variables between patients receiving FFP- or SD-treated plasma during OLT, but α_2-antiplasmin levels were not determined in their study. Hyperfibrinolytic problems were not mentioned in the article, probably because of standard prophylactic use of antifibrinolytic drugs in the participating centers in the United Kingdom. In our patients with chronic liver disease, α_2-antiplasmin levels were relatively high (0.70 IU/mL) after the induction of anesthesia, in contrast to the markedly reduced α_2-antiplasmin levels reported for patients with advanced liver disease (22,23). Low levels of α_2-antiplasmin in the anhepatic phase and after reperfusion in the ESDEP-treated patients compared with the FFP-treated patients explains the increase in hyperfibrinolysis seen in the former group. At the end of the procedure, α_2-antiplasmin levels were increasing in the patients treated with ESDEP, probably because of increased clearance of t-PA by the donor liver and starting synthesis of α_2-antiplasmin. In accordance with the study of Freeman et al. (21), no differences were found in other coagulation variables, use of blood products, or blood loss between the FFP- and ESDEP-treated patients. However, patients from both groups with hyperfibrinolysis had significantly more

bleeding and transfusion requirements than patients without hyperfibrinolysis.

In summary, the results of this observational study have to be interpreted carefully, because other factors could have caused our findings. However, in the time interval of this study, no changes occurred in our operating or anesthesiology techniques, medical staff, or transfusion protocol. Also, the increased incidence of hyperfibrinolysis was present immediately after switching from FFP to ESDEP. Infusion of SD-treated plasma in patients needing massive transfusion may lead to insufficient levels of α_2-antiplasmin and subsequently to secondary hyperfibrinolysis. This hyperfibrinolysis cannot be corrected with infusion of more SD-treated plasma, because this would dilute the α_2-antiplasmin concentration in the patient to that of ESDEP itself (0.28 IU/L). Therefore, it should be treated with antifibrinolytic medication. The effects of aprotinin on antiplasmin activity, hyperfibrinolysis, and subsequent blood loss have been reported with various outcomes (3,24–27). Considering the significantly larger blood loss in patients with hyperfibrinolysis in our study, routine administration of antifibrinolytic drugs when using SD virus-inactivated plasma is suggested.

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References

1. Legnani C, Palareti G, Rodorigo G, et al. Protease activities, as well as plasminogen activators, contribute to the "lytic" state during orthotopic liver transplantation. Transplantation 1993; 56:568–72.
2. Dzik WH, Arkin CF, Jenkins RL, Stump DC. Fibrinolysis during liver transplantation in humans: role of tissue-type plasminogen activator. Blood 1988;71:1090–5.
3. Patrassi GM, Viero M, Sartori MT, et al. Aprotinin efficacy on intraoperative bleeding and transfusion requirements in orthotopic liver transplantation. Transfusion 1994;34:507–11.
4. Bakker CM, Metselaar HJ, Groenland TN, et al. Increased tissue-type plasminogen activator activity in orthotopic but not heterotopic liver transplantation: the role of the anhepatic period. Hepatology 1992;16:404–8.
5. Beeck H, Hellstern P. In vitro characterization of solvent/detergent-treated human plasma and of quarantine fresh frozen plasma. Vox Sang 1998;74:219–23.
6. Hellstern P, Sachse H, Schwinn H, Oberfrank K. Manufacture and in vitro characterization of a solvent/detergent-treated human plasma. Vox Sang 1992;63:178–85.
7. Kohler M, Wieding JU. Virusinaktiviertes Plasma. Infusionsther Transfusionsmed 1994;21:73–6.
8. Kang YG, Martin DJ, Marquez J, et al. Intraoperative changes in blood coagulation and thrombelastographic monitoring in liver transplantation. Anesth Analg 1985;64:888–96.
9. McNicol PL, Liu G, Harley ID, et al. Patterns of coagulopathy during liver transplantation: experience with the first 75 cases using thrombelastography. Anaesth Intensive Care 1994;22: 659–65.
10. Steib A, Gengenwin N, Freys G, et al. Predictive factors of hyperfibrinolytic activity during liver transplantation in cirrhotic patients. Br J Anaesth 1994;73:645–8.
11. Segal HC, Hunt BJ, Cottam S, et al. Fibrinolytic activity during orthotopic liver transplantation with and without aprotinin. Transplantation 1994;58:1356–60.
12. Horowitz B, Lazo A, Grossberg H, et al. Virus inactivation by solvent/detergent treatment and the manufacture of SD-plasma. Vox Sang 1998;74:203–6.
13. Biesert L, Suhartono H. Solvent/detergent treatment of human plasma: a very robust method for virus inactivation—validated virus safety of OCTAPLAS. Vox Sang 1998;74:207–12.
14. Robbie LA, Booth NA, Croll AM, Bennett B. The roles of alpha 2-antiplasmin and plasminogen activator inhibitor 1 (PAI-1) in the inhibition of clot lysis. Thromb Haemost 1993;70:301–6.
15. Weitz JI, Leslie B, Hirsh J, Klement P. Alpha 2-antiplasmin supplementation inhibits tissue plasminogen activator-induced fibrinogenolysis and bleeding with little effect on thrombolysis. J Clin Invest 1993;91:1343–50.
16. Collen D, Lijnen HR. Molecular basis of fibrinolysis, as relevant for thrombolytic therapy. Thromb Haemost 1995;74:167–71.
17. Rao AK, Pratt C, Berke A, et al. Thrombolysis in Myocardial Infarction (TIMI) Trial: phase I—hemorrhagic manifestations and changes in plasma fibrinogen and the fibrinolytic system in patients treated with recombinant tissue plasminogen activator and streptokinase. J Am Coll Cardiol 1988;11:1–11.
18. Weitz JI, Leslie B, Ginsberg J. Soluble fibrin degradation products potentiate tissue plasminogen activator-induced fibrinogen proteolysis. J Clin Invest 1991;87:1082–90.
19. Inbal A, Epstein O, Blickstein D, et al. Evaluation of solvent/detergent treated plasma in the management of patients with hereditary and acquired coagulation disorders. Blood Coagul Fibrinolysis 1993;4:599–604.
20. Baudoux E, Margraff U, Coenen A, et al. Hemovigilance: clinical tolerance of solvent-detergent treated plasma. Vox Sang 1998; 74:237–9.
21. Freeman JW, Williamson LM, Llewelyn C, et al. A randomized trial of solvent/detergent and standard fresh frozen plasma in the treatment of the coagulopathy seen during orthotopic liver transplantation. Vox Sang 1998;74:225–9.
22. Aoki N, Yamanaka T. The alpha2-plasmin inhibitor levels in liver diseases. Clin Chim Acta 1978;84:99–105.
23. Teger-Nilsson AC, Gyzander E, Myrwold H, et al. Determination of fast-acting plasmin inhibitor (alpha2-antiplasmin) in plasma from patients with tendency to thrombosis and increased fibrinolysis. Haemostasis 1978;7:155–7.
24. Marcel RJ, Stegall WC, Suit CT, et al. Continuous small-dose aprotinin controls fibrinolysis during orthotopic liver transplantation. Anesth Analg 1996;82:1122–5.
25. Kufner RP. Antifibrinolytics do not reduce transfusion requirements in patients undergoing orthotopic liver transplantation. Liver Transpl Surg 1997;3:668–74.
26. Garcia-Huete L, Domenech P, Sabate A, et al. The prophylactic effect of aprotinin on intraoperative bleeding in liver transplantation: a randomized clinical study. Hepatology 1997; 26:1143–8.
27. Porte RJ, Molenaar IQ, Begliomini B, et al. Aprotinin and transfusion requirements in orthotopic liver transplantation: a multicentre randomised double-blind study. Lancet 2000;355: 1303–9.