Effectiveness of Aprotinin in Orthotopic Liver Transplantation

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Hemostatic disorders are a principal feature of orthotopic liver transplantation (OLT) and still a significant cause of intraoperative and postoperative blood loss.[1] There is a well-recognized correlation between intraoperative blood loss and subsequent postoperative morbidity and mortality.[2]

Hyperfibrinolysis or disseminated intravascular coagulation (DIC) seem to play an important role in intraoperative bleeding. The most striking hemostatic abnormalities during OLT occur late in the anhepatic phase and immediately after graft revascularization.[3–6] At present, there is no standard treatment for these disorders.[7] Epsilon-aminocaproic acid has been administered without reduction in blood requirements, while antifibrinolytic agents have been used with some degree of success.[8]

Aprotinin is a naturally occurring polypeptide that acts as an inhibitor of human plasmin, trypsin, and kallikrein and can inhibit the development of fibrinolysis.[9] Aprotinin has also proved to be useful in reducing operative bleeding in cardiac surgery,[10] and the initial results in OLT are promising.[3,11,12] The aim of this preliminary study was to evaluate the effectiveness of aprotinin against blood loss during OLT.

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PATIENTS AND METHODS

Twenty-eight consecutive patients undergoing OLT were studied. Thirteen patients were given aprotinin (Trasylol, Bayer AG, Leverkusen, Germany) at a loading dose of 2 million kallikrein inactivator units (KIU) administered as a bolus, followed by a continuous intravenous infusion of 0.5 million KIU/hour until the end of surgery. Fifteen patients did not receive aprotinin and

TABLE 1. Characteristics of Patients

	Aprotinin Group	*Control Group*
No. of patients	13	15
Age (years)	47.1 ± 10.0	45.4 ± 10.9
Sex (M/F)	9/4	9/6
Etiology		
Liver cirrhosis	12	12
Miscellaneous	1	3
Child's stage		
A	1	2
B	6	7
C	6	6
Hematocrit (%)	30.3 ± 4.1	32.3 ± 6.1
Prothrombin activity (%)	38.5 ± 12.8	40.7 ± 16.0
aPTT (sec)	54.6 ± 29.5	44.5 ± 17.0
Platelet counts ($\times 10^9$/l)	59.7 ± 29.8	80.6 ± 74.5
D-Dimer (ng/ml)	276.9 ± 62.1	306.7 ± 54.7
Fibrinogen (mg/dl)	126.1 ± 45.3	185.9 ± 110.1

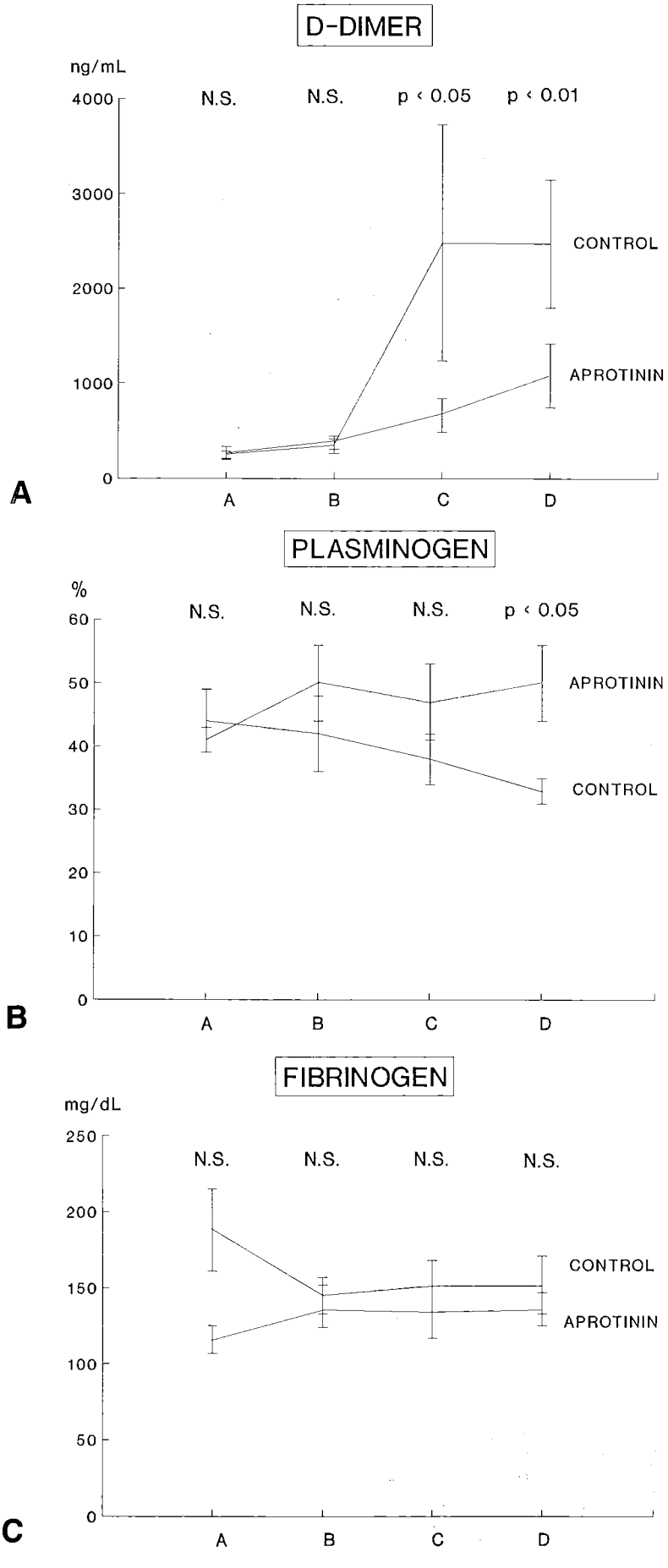


FIG. 1. Values of D-Dimer (Panel A), Plasminogen (Panel B), and Fibrinogen (Panel C) during Surgery (Mean ± SD). Blood samples were obtained: (A) immediately after anesthesia induction (before aprotinin administration in the treated group); (B) before portal vein occlusion; (C) before graft revascularization; and (D) at the end of surgery.

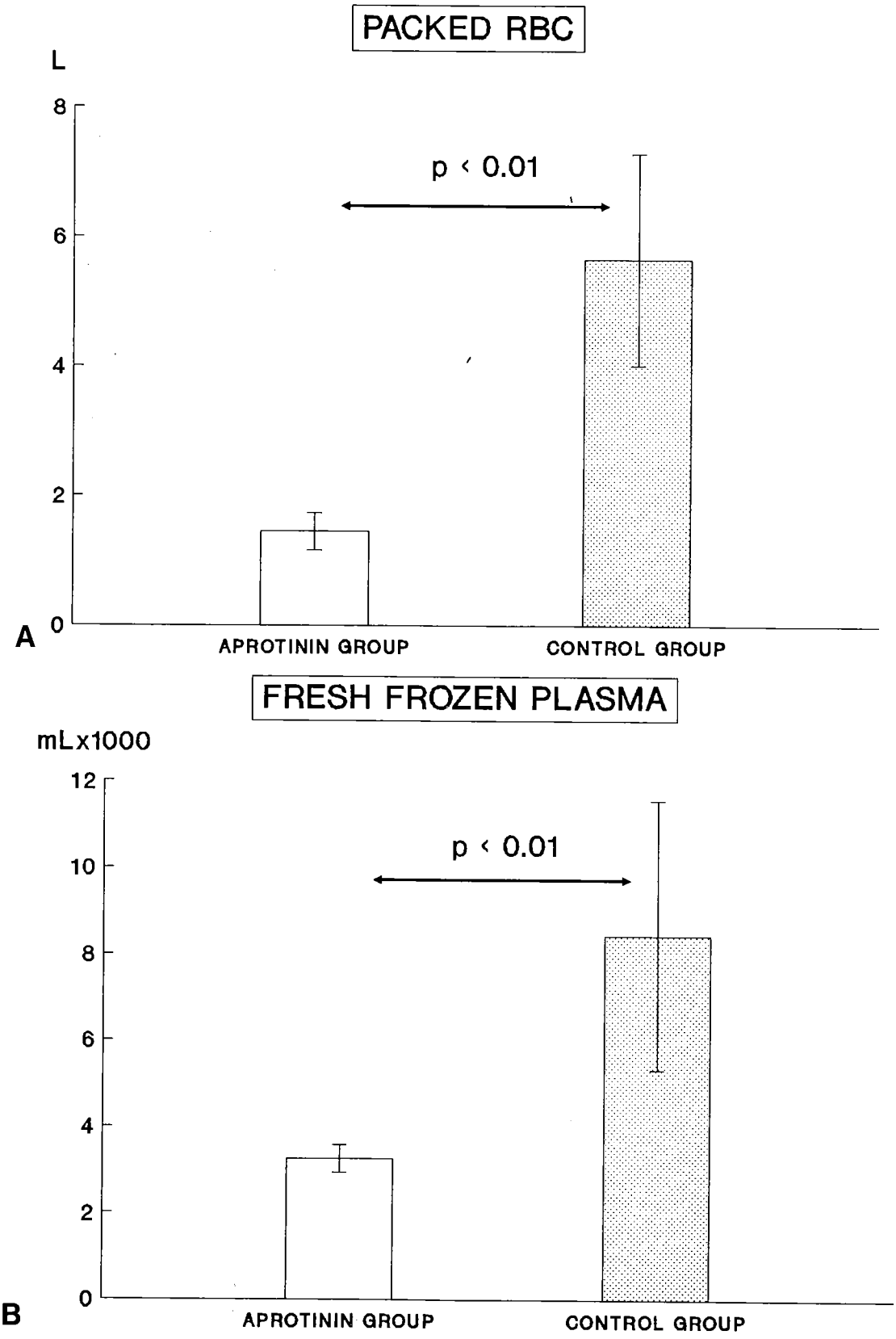
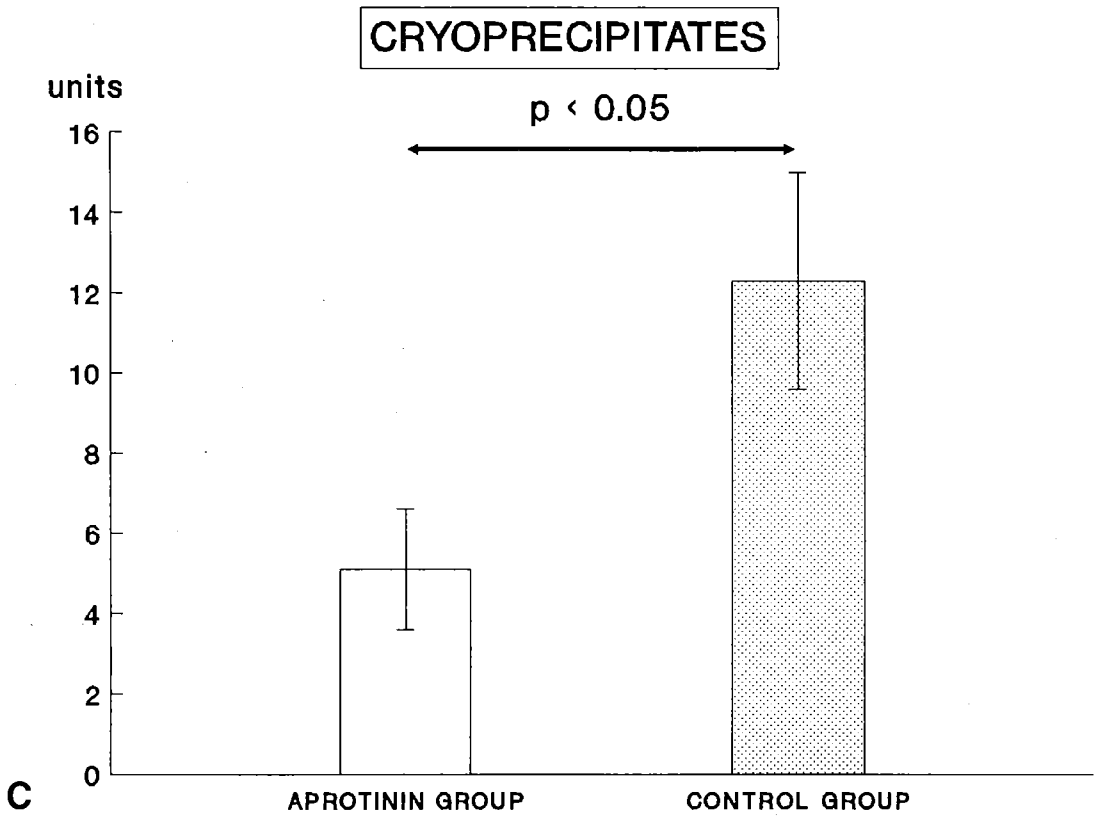


FIG. 2. Intraoperative Transfusional Requirements for Packed Red Blood Cells (Panel A) and Fresh Frozen Plasma (Panel B).



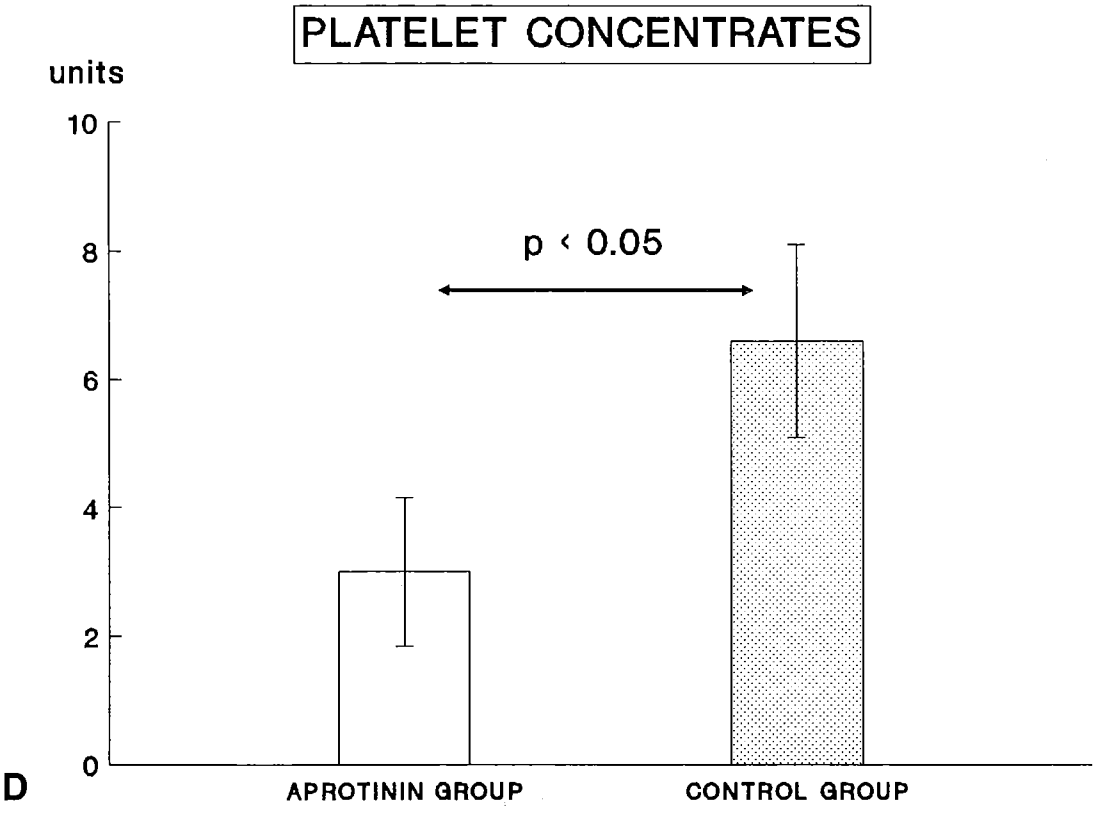


FIG. 2. (Continued). Intraoperative Transfusional Requirements for Cryoprecipitate (Panel C), and Platelet Concentrates (Panel D) (Mean ± SD).

constituted the control group. There were no significant differences between the groups with regard to patient age, preoperative diagnosis, Child-Pugh status, or hemostatic variables (Table 1).

All OLT procedures were performed by a single surgical team, and no form of venovenous bypass was used in any of the patients. For the purpose of this study, analytical determinations were performed on blood samples obtained immediately after the induction of anesthesia, before occlusion of the portal vein, before revascularization of the graft (end of the anhepatic period), and at the end of surgery. The intraoperative requirements for packed red blood cells, fresh frozen plasma, platelet concentrates, cryoprecipitate, and albumin were recorded.

In addition to the standard clotting tests, fibrinolysis was monitored by determining fibrinogen (Clauss), D-dimer (semiquantitative latex test, Ortho Dimer Test), α_2-antiplasmin and plasminogen (chromogenic substrates).

Data are reported as mean ± SD. The Mann-Whitney U test was used for statistical comparisons between groups.

RESULTS

Standard Hemostatic Tests

Hematocrit values, prothrombin times, activated partial thromboplastin times, and platelet counts showed no significant differences between the control and aprotinin groups throughout the different operative periods.

Study of Hyperfibrinolytic Activity

Compared with the control group, patients given aprotinin showed significantly lower levels of D-dimer from the anhepatic phase to the end of surgery (Fig. 1A). This was associated with a significantly higher level of plasminogen in the aprotinin group in the final period (Fig. 1B).

α_2-Antiplasmin was significantly higher in the aprotinin-treated patients during the entire surgical time ($p < 0.05$ in all surgical periods). No significant differences between the groups were observed in fibrinogen levels (Fig. 1C).

The intraoperative requirements for packed red blood cells ($p < 0.01$) (Fig. 2A), fresh frozen plasma ($p < 0.01$) (Fig. 2B), cryoprecipitate ($p < 0.05$) (Fig. 2C), and platelet concentrates ($p < 0.05$) (Fig. 2D) were significantly lower in the aprotinin than in the control group.

High doses of aprotinin were well tolerated by all patients without adverse effects.

CONCLUSIONS

The administration of aprotinin was associated with decreased fibrinolytic activity from the anhepatic phase to the end of the operative time. Patients receiving aprotinin required markedly lower intraoperative volumes of blood and blood derivatives. It is suggested that the use of aprotinin during OLT may be useful in preventing bleeding, thus limiting the administration of blood products to these patients. A randomized controlled trial is needed to definitely establish the indication for aprotinin in OLT.

REFERENCES

1. Bismuth H, BG Ericzon, K Rolles, D Castaing, YB Otte, B Ringe, M Sloof: Hepatic transplantation in Europe. First report of the European Liver Transplantation Registry. Lancet 2:674–676, 1987.
2. Butler P, L Israel, J Nusbacher, RI Jenkins Jr, TE Starzl: Blood transfusion in liver transplantation. Transfusion 25:120–123, 1985.
3. Grosse H, W Lobbes, M Frambach, O von Broen, B Ringe, M Barthels: The use of high dose aprotinin in liver transplantation. The influence of fibrinolysis and blood loss. Thromb Res 63:287–297, 1991.
4. Groth CG, L Pechet, TE Starzl: Coagulation during and after orthotopic transplantation of the human liver. Arch Surg 98:31–34, 1969.
5. Porte RJ, FA Bontempo, EAR Knot, JH Lewis, YG Kang, TE Starzl: Tissue type-plasminogen-activator associated fibrinolysis in orthotopic liver transplantation. Transplant Proc 21:35–42, 1989.
6. Dzik WH, CF Arkin, RL Jenkins, DC Stump: Fibrinolysis during liver transplantation in humans. Role of tissue-type plasminogen activator. Blood 71:1090–1095, 1988.
7. Porte RJ, FA Bontempo, EAR Knot, JH Lewis, YG Kang, TE Starzl: Systemic effects of tissue plasminogen activator-associated fibrinolysis and its relation to thrombin generation in orthotopic liver transplantation. Transplantation 47:978–984, 1989.
8. Kang YG, JH Lewis, A Navalgund, MW Russell, FA Bontempo, LS Niren, TE Starzl: Epsilon-aminocaproic acid for treatment of fibrinolysis during liver transplantation. Anesthesiology 66:766–773, 1987.
9. Fritz H, G Wunderer: Biochemistry and application of aprotinin, the kallikrein inhibitor from bovine organs. Drugs Res 33:479–495, 1983.
10. Royston D, KM Taylor, BP Bidstrup, RN Sapsford: Effects of aprotinin on need for blood transfusion after repeat open-heart surgery. Lancet 1:1289–1291, 1987.
11. Mallett S, K Rolles, D Cox, A Burroughs, B Hunt: Intraoperative use of aprotinin (Trasylol) in orthotopic liver transplantation. Transplant Proc 23:1931–1932, 1991.
12. Cottam S, B Hunt, H Segal, R Ginsburg, D Potter: Aprotinin inhibits tissue plasminogen activator-mediated fibrinolysis during orthotopic liver transplantation. Transplant Proc 23:1933, 1991.