The intra-operative use of trasylol (aprotinin) in liver transplantation

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Received December 11, 1990/Received after revision May 23, 1991/Accepted June 6, 1991

Abstract. Aprotinin has been reported to reduce blood loss in difficult cases requiring cardiopulmonary bypass surgery and more recently in liver transplantation. Over a 9-month period we compared the effects of an intra-operative infusion of aprotinin on transfusion requirements and coagulation profiles in 12 patients undergoing liver transplantation for end-stage cirrhosis with an equal number of consecutive transplants in patients with similar pathology who did not receive aprotinin. Transfusion of blood and blood products was reduced to one-third in the aprotinin-treated group. Operative time was also significantly reduced, as was ICU stay post-operatively. Aprotinin profoundly inhibits fibrinolysis and this is likely to be the major effect by which blood loss is reduced. Thromboelastography revealed severe fibrinolytic changes in the anhepatic stage in 4 of 6 controlled patients; this accelerated in 3 following reperfusion of the new graft. By contrast, only 1 patient of 12 in the aprotinin-treated group showed fibrinolytic activity in the anhepatic period, and none showed evidence of fibrinolysis following reperfusion of the new graft.

Key words: Liver transplantation, trasylol – Trasylol, liver transplantation – Aprotinin, liver transplantation

Fibrinolysis is likely to result from an imbalance of inhibitors and activators of the fibrinolytic system. End-stage cirrhotics undergoing orthotopic liver transplantation frequently show a decreased hepatic clearance of circulating tissue plasminogen activator (tPA) and also decreased synthesis of plasminogen activator inhibitor (PAI) [5].

Trasylol (aprotinin; Bayer, Newbury, UK) is a serine protease inhibitor derived from bovine lung and apocrine tissue. In 1964 Tice et al. [7] demonstrated the efficacy of aprotinin in the prevention and inhibition of fibrinolysis in patients undergoing cardiopulmonary bypass. Royston et al. [6] reported the effect of aprotinin in reducing transfusion requirements during open-heart surgery.

In liver transplantation, Neuhaus et al. [4] have reported a reduction in intra-operative bleeding and fibrinolysis with the use of aprotinin.

We have conducted a pilot study of the effect of trasylol (aprotinin) on blood transfusion requirements and coagulation during liver transplantation. Specifically studied were the effects of aprotinin on:

2. The incidence and severity of fibrinolysis during the operative procedure, as measured by thromboelastography and specific factor assays.
3. The length of the operative procedure.
4. The length of the stay in the intensive care unit (ICU).
Patients and methods

Twenty-four consecutive patients undergoing liver transplantation for end-stage cirrhosis were studied over a 9-month period. The first 12 patients served as controls and did not receive intra-operative aprotinin. The second cohort of 12 patients (the study group) received intra-operative infusions of aprotinin as detailed below. All transplant procedures were performed by a single experienced surgeon. A standard anaesthetic technique was used. No form of extracorporeal bypass was used in any of the patients.

Three patients in the study group and three patients in the control group were permanently hospitalized before transplantation; the remaining patients were called in from home. Ethics committee approval and relevant patient informed consent were obtained.

Patients in the study group were given a loading dose of 2 million kallikrein inhibitory units (KIU) of preservative-free aprotinin via a central line. A infusion of 500 000 KIU per hour was then continued until the patient was transferred to the ICU. In addition, 70 000 KIU was added to each unit of blood transfused intra-operatively.

Fresh frozen plasma (FFP) and blood in a ratio of 1:1 were transfused to maintain clotting factors and a haematocrit of 30%. Platelets and cryoprecipitate were given as indicated by laboratory and thromboelastographic results.

Operative procedure

For comparative purposes, the operative procedure was divided into three stages. Stage 1 was pre-anhepatic (first incision to recipient hepatectomy), stage 2 was anhepatic and stage 3 was post-anhepatic (reperfusion of new graft to skin closure). Blood samples were taken in each case at the following times: (1) Anaesthesia + 30 min, (2) Stage 1 + 30 min, (3) Stage 2 + 10 min, (4) Stage 3 + 10 min, (5) Stage 3 + 5 min, (6) Stage 3 + 30 min, (7) Stage 3 + 60 min, (8) Stage 3 + 120 min.

Each blood sample was analysed for: (1) haemoglobin, (2) prothrombin time/international normalised ratio (INR), (3) partial thromboplastin time (PTT), (4) platelets, (5) potassium, (6) sodium, (7) calcium, (8) glucose, and (9) thromboelastography.

In a smaller patient group, specific factor assays, tPA, antiplasmin and PAI were measured.

Thromboelastography

Thromboelastography (TEG) is a technique that measures the viscoelastic properties of clot, giving information on the whole coagulation process from a single blood sample. Within 20–30 min it is possible to identify clotting factor activity, platelet function and any significant fibrinolytic process (Fig. 1). It has obvious applications in settings where there are potentially a multitude of haemostatic defects requiring rapid on-site diagnosis and intervention. It is now routinely used in many centres for the monitoring of coagulation during liver transplantation [3] and in cardiac surgery.

Post-operative procedure

Patients were electively ventilated in the ICU for a minimum period of 24 h. Following endotracheal extubation, patients who were haemodynamically stable with good renal and respiratory function were discharged from the ICU to a surgical ward.

Statistics

The Mann-Whitney U-test was used, on advice of our Department of Clinical Epidemiology and Statistics, as the most appropriate and powerful non-parametric test for data from two populations of this size.

Results

Haematological data (Fig. 2)

Red blood cell requirements. A mean of 23.6 units with a median of 21.5 units was transfused in the untreated (control) group (range 6–55). In the aprotinin group a mean of