Heparin and Thromboelastography in Liver Transplantation for a Patient with von Willebrand’s Disease

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THE role of heparin in impaired hemostasis during orthotopic liver transplantation (OLT), either exogenously derived from prior administration to the donor or endogenously derived from the donor liver, is controversial.1,2 A report of improved clinical and laboratory indexes of bleeding after reperfusion administration of protamine was not accompanied by objective evidence of the presence of heparin,3 although Kang has promoted comparison of the untreated and protamine-treated thromboelastograph.4 Because the use of bacterial derived heparinase has been reported in cardiac surgery with the activated clotting time (ACT)5 and thromboelastography,6 heparinase was used to assess potential heparin effect with the thromboelastograph during OLT in a patient with type IIA von Willebrand’s disease (vWD), when potential difficulty was expected in the diagnosis of heparin effect after reperfusion.

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Case Report

A 46-yr-old woman (weight 53.5 kg, height 1.5 m) with primary biliary cirrhosis presented for OLT. She had portal hypertension that required previous sclerotherapy for bleeding esophageal varices and a transjugular intrahepatic portosystemic shunt (TIPS) procedure. She had vWD type IIA, the diagnosis having been made on the basis of normal von Willebrand factor (vWF) antigen level, low ristocetin cofactor activity indicative of low vWF function, and no platelet aggregation in response to low concentrations of ristocetin.7

At preoperative assessment, apart from the stigmata of end-stage liver disease, the patient had poor dentition, with slight bleeding from the base of the left upper premolar tooth without other sites of hemorrhage, and no evidence of cardiorespiratory disease. The patient had received one-deamino-8-D-arginine vasopressin (DDAVP) for oral bleeding some years previously but had not reported bleeding complication with the TIPS procedure. Laboratory results included prothrombin time (PT) 11.7 s (normal range 11.1–13.1 s), partial thromboplastin time (PTT) 40.3 s (25–34 s), platelet count 110 × 10^9 mm$^{-3}$, hematocrit 31.6%, and normal serum electrolytes.

Prophylactic DDAVP (20 µg, intravenous) was administered before anesthetic induction because of the anticipated bleeding and the previous reported use. Standard anesthetic agents, adjuvants (sodium thiopental, fentanyl, pancuronium, and noflurane), and monitoring were used.

Thromboelastgraphs were recorded concurrently with and without heparinase (4 IU tube$^{-1}$). A 1-ml blood sample was introduced into the heparinase tube, mixed by inversion, incubated for 5 min, and 0.36 ml withdrawn for insertion into the thromboelastograph cuvette. No heparin was used in the flush solution for invasive monitors or during venovenous bypass, and the donor liver was flushed with 500 ml albumin (5%) before portal vein anastomosis. Perioperative hematologic variables are presented in table 1.

Discussion

This report demonstrates how thromboelastography from Flavobacterium species can cleave the alpha chains of von Willebrand factor. This has been useful for monitoring in cardiopulmonary bypass and whole heart forpropranolol to determine end-tidal concentrations during bypass. Thromboelastographs were performed concurrently with and without heparinase (4 IU tube$^{-1}$). A 1-ml blood sample was introduced into the heparinase tube, incubated for 5 min, and 0.36 ml withdrawn for insertion into the thromboelastograph cuvette. No heparin was used in the flush solution for invasive monitors or during venovenous bypass, and the donor liver was flushed with 500 ml albumin (5%) before portal vein anastomosis. Perioperative hematologic variables are presented in table 1.
### Table 1. Perioperative Hematologic Values

<table>
<thead>
<tr>
<th>Condition</th>
<th>PT (s)</th>
<th>PTT (s)</th>
<th>TT (Patient/Control, s)</th>
<th>Fibrinogen (mg/dl)</th>
<th>Platelets (x10^3/mm^3)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dissection</td>
<td>11.9</td>
<td>36.6</td>
<td>20.5/21</td>
<td>259</td>
<td>69</td>
</tr>
<tr>
<td>Anephric</td>
<td>11.8</td>
<td>36.3</td>
<td>24/21</td>
<td>198</td>
<td>51</td>
</tr>
<tr>
<td>Postreperfusion</td>
<td>13</td>
<td>41.4</td>
<td>23.5/20</td>
<td>190</td>
<td>39</td>
</tr>
<tr>
<td>Normal</td>
<td>11.1−13.1</td>
<td>25−34</td>
<td>18−22</td>
<td>170−410</td>
<td>133−333</td>
</tr>
</tbody>
</table>

PT = prothrombin time; PTT = partial thromboplastin time; TT = thrombin time.

Thromboplasty traces with heparinase before the anephric phase were unchanged from native blood, and the preanephric PTT prolongation was compatible with WtD. However, immediately after reperfusion, the essentially straight-line native thromboplasty graph (fig. 1A) suggested heparinlike effect that was corrected in the heparinase trace (fig. 1B). Administration of protamine (50 mg, intravenous) restored the native thromboplasty graph trace (fig. 1C) to that of the heparinase-treated sample.

Estimated blood loss was 7,000 ml, and blood product administration was guided by clinical inspection, thromboplasty graph, and standard laboratory coagulation parameters. Fifteen units of packed erythrocytes and 11 “jumbo” units of fresh-frozen plasma (volume 600–650 ml) were used. Two six-pack units of platelets and one six-pack unit of cryoprecipitate were administered toward the end of surgery for persistent thrombocytopenia and oozing. One six-pack of cryoprecipitate had been given prophylactically before incision. Postoperatively, additional platelets and cryoprecipitate were administered in the intensive care unit to correct thrombocytopenia and the prolonged PTT. An episode of suspected organ rejection was treated with plasmapheresis in addition to immunosuppression; the patient improved slowly and was discharged on postoperative day 30.

#### Discussion

This report documents the use of heparinase-guided thromboplasty during OLT. Heparinase, derived from *Flavobacterium heparinum*, has been shown to cleave the alpha glycosidic linkages in heparin with loss of associated anticoagulant effect.8 Use of heparinase has been reported as an aid to coagulation monitoring in cardiac surgery, with potential implications for protamine dosage. Heparinase added to the ACT5 and whole blood PT and activated PTT has been used to determine effective baseline coagulation parameters during bypass, and a heparinase-modified thromboplasty graph was used to define coagulation indexes.9 Tuman et al. concluded that the heparinase effectively removed small quantities of heparin associated with contamination without completely normalizing the thromboplasty R time in the presence of larger heparin doses used for anticoagulation during bypass.6 However, Despotis et al. found heparinase to be effective in reversing large amounts of heparin in plasma from cardiac surgical patients, as measured by PT and PTT.7

The presence of heparin after reperfusion of the donor liver during OLT has been suggested using the PTT and thrombin time (TT).9 A possible source is heparin sequestered in the liver after administration to the donor before organ procurement, although release of endogenous heparin or heparinlike substances from the donor liver endothelium has been hypothesized.10 A report documented correction of postreperfusion bleeding and thromboplasty abnormalities in two patients with 50 mg protamine.3 Although the ACT is insensitive to low concentrations of heparin, and laboratory measures such as the PTT and TT are subject to delay, the heparinase-guided thromboplasty offers the advantage of clinically relevant information within minutes.

The risk of heparin contamination in this patient was eliminated by excluding heparin from the invasive cannulae flush tubing, by drawing arterial blood gas samples (heparin-containing syringe) after thromboplasty samples, and by flushing the donor liver before portal vein anastomosis to remove exogenously derived heparin. The absence of any difference in the native and heparinase thromboplasty graph parameters during the preanephric and initial anephric phases supports the absence of measurable heparin effect. The marginal PTT prolongation present before induction did not change significantly and was accompanied by stable TTs, also suggesting heparin absence. However, a significant effect compatible with heparin was demonstrated in the postreperfusion thromboplasty studies with further PTT and marginal TT prolongation. The heparinase-treated thromboplasty showed no
CASE REPORTS

Fig. 1. (A) Native blood thrombelastography trace immediately after reperfusion. Patient values (top row) and normal ranges (bottom row) below (each figure). LY 30 and LY 60 are percent fibrinolysis at 0.5 and 1 h, respectively. (B) Heparinase thrombelastography trace immediately after reperfusion. Patient values and normal ranges below. Thrombelastography index is the mathematically derived index of R, K times, angle (Ang), and maximum amplitude (MA). (C) Native blood thrombelastography trace immediately after systemic protamine administration.

Anesthesiology. V 84, No 5, May 1996

sign of coagulation factor or platelet dysfunction, whereas the native thrombelastography trace demonstrated negligible clot formation. Protamine (50 mg, intravenous) was administered as soon as the heparinase trace was seen, with dramatic resolution of native thrombelastography parameters and surgical oozing.

In a patient with altered baseline coagulation parameters, objective evidence of heparin-like effect and thrombelastography-guided protamine therapy allowed rapid correction of one of the factors complicating postreperfusion bleeding. Although cryoprecipitate and platelet transfusions were required toward the end of surgery, the heparinase-thrombelastography prevented inappropriate blood product exposure for the immediate postreperfusion straight-line thrombelastography trace.

Although the perioperative management of von Willebrand’s disease has been reviewed, recent developments are of interest to anesthesiologists. Routine use of DDAVP is not recommended in the absence of individual patient testing for DDAVP response. Its use is controversial in type IIB disease and of no value in type II. DDAVP may be effective in some type IIA patients and was administered initially in this case on the basis of previous use by the patient. Thrombelastography traces were not performed before and after DDAVP administration.

Although cryoprecipitate contains sufficient factor VIII/vWF to be an effective treatment, concern about viral transmission has led to the use of factor VIII:C concentrates for vWD. Reports document the successful use of both Humate-P and Koate (55, 56) (containing a solvent and detergent to inactivate viruses), even though there is a relative lack of high molecular weight von Willebrand factor multimers in the latter product. Both products have normalized laboratory measures of platelet and vWF activity and decreased bleeding, and both have been used prophylactically in vWD patients undergoing surgery. Perioperative cryoprecipitate was used in this case instead of factor VIII products because of unawareness of these developments.

This case of OLT in a patient with vWD is an initial report of the successful use of the heparinase-treated thrombelastograph in assessment of coagulation in liver transplantation. Further study will be required to reproduce the effects of the heparinase-treated thrombelastograph, compare results with traditional tests for heparin presence (ACT, PTI, heparin concentra-
CASE REPORTS

Cervical Dural Puncture in a Neonate: A Rare Complication of Internal Jugular Venipuncture

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CENTRAL venous catheterization via the internal jugular vein (IJV) is used widely for pressure monitoring and drug therapy. Although various complications of IJV catheterization have been described, dural puncture has not been reported. We describe dural puncture during internal jugular venipuncture in a neonate undergoing cardiac surgery.

Case Report

A 16-o-day-old male with a diagnosis of corrected transposition of the great arteries and left-sided atrioventricular valve atresia was...