Liver Transplantation in Hemophilia A

By Franklin A. Bontempo, Jessica H. Lewis, Toni J. Gorenc, Joel A. Spero, Margaret V. Ragni, J.P. Scott, and Thomas E. Starzl

Four patients with hemophilia A have undergone liver transplantation in our institution, three successfully. The first was a 21-year-old man with chronic active hepatitis (CAH) in whom the effects of previous abdominal operations prevented the satisfactory technical insertion of the new liver. He died intraoperatively. The second patient was a 15-year-old boy with CAH who began to synthesize factor VIII coagulant activity (F VIII:C) within 18 hours of successful liver transplantation and has continued to do so for almost 2 years (F VIII:C range 0.89 to 3.20 U/mL). The first 2 months of his postoperative course were complicated by infections, but since that time he has done well and has returned to school. The third patient was a 48-year-old man with portal fibrosis and severe ascites. He synthesized F VIII:C (range 0.96 to 1.50 U/mL) within six hours after reestablishment of circulation through the new liver. His postoperative course was complicated by numerous infections, and he died with sepsis and an acquired immunodeficiency-like syndrome 4 months after transplantation. The fourth patient was a 47-year-old mild hemophiliac with CAH who produced adequate factor VIII:C levels following transplantation (range 0.79 to 2.80 U/mL). These patients demonstrate that liver transplantation in hemophiliacs with end-stage liver disease may be lifesaving and resolve in correction of the F VIII:C deficiency and associated hemorrhagic tendency.

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Table 1. Coagulation Studies

<table>
<thead>
<tr>
<th>Test</th>
<th>Normal Range</th>
<th>Patient 1</th>
<th>Patient 2</th>
<th>Patient 3</th>
<th>Patient 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prothrombin time (s)</td>
<td>10-13</td>
<td>16.6</td>
<td>10.9</td>
<td>11.1</td>
<td>14.4</td>
</tr>
<tr>
<td>Activated partial thromboplastin time (s)</td>
<td>24-34</td>
<td>107.0</td>
<td>39.0</td>
<td>31.9</td>
<td>53.9</td>
</tr>
<tr>
<td>Thrombin time (s)</td>
<td>13-18</td>
<td>40.4</td>
<td>30.5</td>
<td>13.0</td>
<td>27.5</td>
</tr>
<tr>
<td>Reptilase time (s)</td>
<td>13-18</td>
<td>50.4</td>
<td>35.1</td>
<td>—</td>
<td>33.6</td>
</tr>
<tr>
<td>Euglobulin lysis time (min)</td>
<td>120 or &gt;</td>
<td>90</td>
<td>240</td>
<td>240</td>
<td>15</td>
</tr>
<tr>
<td>Ethanol gel (0-4)</td>
<td>0</td>
<td>0</td>
<td>2</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Wellcotest (µg/mL)</td>
<td>0</td>
<td>0</td>
<td>&gt;40</td>
<td>&gt;10&lt;40</td>
<td>0</td>
</tr>
<tr>
<td>Staph clumping titer</td>
<td>1-4</td>
<td>0</td>
<td>0</td>
<td>8</td>
<td>128</td>
</tr>
<tr>
<td>Platelet count (10^3/µL)</td>
<td>150-450</td>
<td>73</td>
<td>344</td>
<td>414</td>
<td>130</td>
</tr>
</tbody>
</table>

*Date of surgery.
†Dates of tests.

thereafter remained normal or supranormal. On the ninth postoperative day he underwent revision of the bile duct reconstruction (initially performed during the transplantation), and on the 28th postoperative day a subphrenic abscess was drained. Both procedures were performed without F VIII replacement therapy, and no excess bleeding was encountered. Pre-operative and postoperative coagulation findings are shown in Tables 1 and 2.

Six weeks postoperatively he was discharged, and since that time he has maintained F VIII:C levels of 0.89 to 3.20 U/mL. He was given 20 vials (100 mL) of hepatitis B immune globulin (HBIG) intraoperatively and postoperatively. His HBsAg has remained positive except for several weeks (beginning about five weeks postoperatively) when it was negative and anti-Hbs appeared. Since then he has remained positive for HbsAg, anti-Hbs, and the antibody to delta agent. He returned to temporary employment in the summer of 1985 and returned to school in the fall of 1985.

Patient 3 was a moderately obese, 48-year-old white, severely F VIII:C-deficient hemophiliac on home treatment with F VIII concentrate as needed since 1973. Since that time his bilirubin, SGPT (ALT), and SGOT (AST) had been intermittently elevated and his anti-HBs had been positive. The patient had a history of alcohol abuse in the past but discontinued its use in 1974. Liver biopsy in 1976 showed portal fibrosis with fatty changes and early nodule formation. His liver disease was moderately stable until July of 1985 when there was a marked increase in girth due to development of massive ascites. The spleen was enlarged; the gallbladder was contracted and contained gallstones. Subsequent progressive jaundice, malaise, accumulation of ascites, and poor response to diuretics heralded further clinical deterioration. Pre-operative and postoperative laboratory findings are shown in Tables 1 through 3.

The patient was evaluated favorably for liver transplantation, and the procedure was performed on October 19, 1985. Twelve liters of ascitic fluid were removed. He received 17,290 units of heat-treated F VIII concentrate and ten units of RBCs intraoperatively. Postoperatively the patient received no F VIII concentrate, and his factor VIII:C level ranged from 0.96 to 1.50 U/mL. An episode of postoperative bleeding of unknown cause necessitated a repeat laparotomy. No excessive operative bleeding was encountered, and no F VIII concentrate was required. The patient suffered a mild rejection crisis and was successfully treated with OKT3 (Ortho Pharmaceuticals, Raritan, NJ) monoclonal antibody (MoAb) therapy. The rejection crisis was followed by pneumocystis carinii pneu-

Table 2. Coagulation Factor Assays (Pre- and Post-Liver Transplant)

<table>
<thead>
<tr>
<th>Factor</th>
<th>Pre</th>
<th>Post</th>
</tr>
</thead>
<tbody>
<tr>
<td>VIII:C</td>
<td>3/8/85</td>
<td>3/19/85</td>
</tr>
<tr>
<td>vWF</td>
<td>10.0</td>
<td>3.68</td>
</tr>
<tr>
<td>RCF</td>
<td>3.75</td>
<td>4.64</td>
</tr>
<tr>
<td>TXA2</td>
<td>0.11</td>
<td>1.20</td>
</tr>
<tr>
<td>IXA2</td>
<td>0.11</td>
<td>1.00</td>
</tr>
<tr>
<td>XI</td>
<td>0.49</td>
<td>0.63</td>
</tr>
<tr>
<td>XII</td>
<td>0.36</td>
<td>0.66</td>
</tr>
</tbody>
</table>

*Normal range, 0.5 to 1.5 U/mL.
†Not treated with F VIII.
‡Treated with F VIII.
monia, which resolved with trimethoprim-sulfamethoxazole therapy. Subsequently a cytomegalovirus infection resolved without treat-
mant of intensive care.

Strategically this patient was treated with OKT3 MoAb, and the patient was discharged approximately 8 weeks postoperatively after maintaining F VIII:C levels between 0.10 U/mL and a history of CAH.

Liver transplantation was performed on June 30, 1986 with 17,120 units of heat-treated F VIII concentrate and eight units of RBCs transfused intraoperative-

No factor VIII replacement was given postoperatively. The patient presented here not only reversed the hepatic failure but also the new liver began synthesizing F VIII:C within four hours after the procedure. His postoperative course was complicated by a mild rejection episode, which was also treated successfully with OKT3 MoAb, and the patient was discharged approximately 8 weeks postoperatively after maintaining F VIII:C levels between 0.79 and 2.80 U/mL.

**DISCUSSION**

Successful liver transplantation in the hemophiliacs presented here not only reversed the hepatic failure but also corrected the coagulation defect of hemophilia A. These results demonstrate that hemophilia should not be a contraindication for the procedure and that resolution of the hemophilia, except for genetic transmissibility, should be expected. Therefore consideration of this procedure as a feasible, albeit difficult option should be given to the small but significant number of hemophiliacs who suffer from end-stage liver disease. The fatal outcome of Patient 1 suggests that scarring and fibrous changes after abdominal surgical procedures, especially shunting procedures and splenectomy, may make liver transplantation difficult or impossible and should be avoided. Whether or not the presence of human immunodeficiency virus (HIV) antibodies in a transplant candidate will alter the selection process remains to be determined. Three of these four patients were HIV antibody positive, and one of the three suffered from opportunistic infections typical of acquired immunodeficiency syndrome (AIDS) or the immunosuppressed post-transplantation state.

**REFERENCES**


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