Liver Transplantation Without the Use of Blood Products

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Objectives: To examine the techniques and the outcome of liver transplantation with maximal conservation of blood products and to analyze the potential benefits or drawbacks of blood conservation and salvage techniques.

Design: Case series survey.

Setting: Tertiary care, major university teaching hospital.

Patients and Methods: Four patients with religious objections to blood transfusions who were selected on the basis of restrictive criteria that would lower their risk for fatal hemorrhage, including coagulopathy, a thrombosed splanchnic venous system requiring extensive reconstruction, active bleeding, and associated medical complications. All patients were pretreated with erythropoietin to increase production of red blood cells. All operations were performed at the same institution, with a 36-month follow-up.

Interventions: Orthotopic liver transplantation that used blood salvage, platelethpheresis, and autotransfusion and the withholding of the use of human blood products with the exception of albumin.

Main Outcome Measures: Survival and postoperative complications, with the effectiveness of erythropoietin and platelethpheresis as secondary measures.

Results: All patients are alive at 36 months after orthotopic liver transplantation. One patient, a minor (13 years of age), was transfused per a state court ruling. Erythropoietin increased the production of red blood cells as shown by a mean increase in hematocrit levels of 0.08. Platelethpheresis allowed autologous, platelet-rich plasma to be available for use after allograft reperfusion. Three major complications were resolved or corrected without sequelae. Only one patient developed postoperative hemorrhage, which was corrected surgically. The mean charge for bloodless surgery was $174,000 for the three patients with United Network for Organ Sharing (UNOS) status 3 priority for transplantation. This result was statistically significant when these patients were compared with all the patients with UNOS status 3 priority during the same period who met the same restrictive guidelines (P<.05). Only 19 of 1009 orthotopic liver transplantations performed at our institution were similar according to the UNOS status and the fulfillment of the guidelines. The mean charge for these comparison patients was $327,000, 3.8% of which was related to transfusions.

Conclusions: Orthotopic liver transplantation without the use of blood products is possible. Blood conservation techniques do not increase morbidity or mortality and can result in fewer transfusion-related, in-hospital charges.

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PATIENTS AND METHODS

PATIENT POPULATION

From October 1990 to July 1993, 1009 transplantations in adult patients were performed at the University of Pittsburgh Medical Center. During this period, four patients who were Jehovah’s Witnesses underwent liver transplantation under a specific protocol geared to perform a successful, bloodless procedure. Characteristics of the four patients are shown in Table 1.

PATIENT SELECTION

All patients were selected and their conditions evaluated by a team consisting of two transplantation surgeons, two anesthesiologists, and a legal representative for the institution. Restrictive guidelines for the bloodless surgery protocol were: (1) hematocrit level of 0.35 or less after erythropoietin therapy; (2) platelet count of less than 100,000 X 10^9/L; (3) prothrombin time of more than 15.0 seconds; (4) known splanchnic venous anatomy that would require extensive vascular reconstruction at the time of transplantation; (5) active bleeding; and (6) renal failure and other major organ dysfunction. Drugs that may inhibit platelet function or coagulation were strictly withheld.

After selection, a meeting was held with the surgical team, family members, religious counsel, and the anesthesiology staff. Treatment options, the patient’s type and severity of liver disease, and the details of the risks and the benefits of transplantation, including the possibility of death, were explained. Acceptable blood volume expanders were discussed with the aid of the patient’s religious counsel. In all cases, the use of albumin, plateleterapheresis, and cell salvage with autotransfusion were acceptable.

PRETRANSPLANTATION MANAGEMENT

The patients were listed for orthotopic liver transplantation by priority status, according to guidelines of the United Network for Organ Sharing (UNOS). Each patient started therapy consisting of recombinant erythropoietin, 50 to 100 U/kg subcutaneously three times a week, and ferrous sulfate Fe 59, 325 mg orally three times a day, to increase production of red blood cells. Phytonadione therapy, 20 mg subcutaneously, was also started to augment coagulation. All blood tests were kept to a minimum, i.e., blood was drawn twice in 6 weeks in pediatric vials, using 1 mL of whole blood for routine laboratory evaluations of hematologic, chemistry, and coagulation status.

INTRAOPERATIVE MANAGEMENT AND OPERATIVE TECHNIQUE

Cold ischemia was kept to a minimum. Only local donors were used. The operating room was kept warm to avoid hypothermia and resultant coagulopathy. All intraoperative blood sampling was also kept to a minimum. Laboratory evaluations included testing for arterial blood gas, electrolytes, and hematocrit levels and thromboelastography. The thromboelastograph (Hemoscope, Hellige, Germany) was used as the primary monitor of coagulation status. Plateletpheresis was performed after induction by phlebotomizing 5 to 7 L of blood at a flow rate. Continued on next page
rate of 60 mL/min and processing through the platelet­
pheresis unit (Hemonetics, Braintree, Mass). We esti­
minated that one pheresis product of 250 to 300 mL con­
tained a platelet count of $3 \times 10^7$/L to $8 \times 10^7$/L, to be infused
after reperfusion.

Filling pressures were optimized during the pheresis
procedure with albumin, crystalloid solutions, and hy­
droxethyl starch. Isovolemic hemodilution was therefore
achieved in conjunction with the phlebotomy for the platelet­
pheresis. Phlebotomized, platelet-poor blood was rein­
fused slowly to maintain oxygen-carrying capacity.

All incisions were made using electrocauterity with a
coagulation mode. The use of laparotomy sponges was kept
to a minimum to allow for the collection of as many red
blood cells as possible before stable clots could form. When
used, the sponges were drained into the field, and the drained
blood was collected with the cell-saver suction. The cell­saver
(Hemonetics) and the Rapid Infusion System (Hemonetics)
were used for the salvage of red blood cells.

The native liver was removed in all patients, with the
piggyback technique used in three patients to avoid dis­
section of the retroperitoneal and retrocaval areas. An argon
beam coagulator (Bircher, Irvine, Calif) was used lib­
erally to cauterize raw surfaces. Venovenous bypass, either
portal, systemic, or combined, was used in all cases.

On reperfusion of the liver and termination of the
venovenous bypass, platelet-rich plasma was slowly re­
turned to the patient. The blood from the venovenous
bypass tubing was drained directly into the patient. This
process returned between 200 and 250 mL of blood per
patient.

All anastomoses were performed in standard fashion.
Extra care was taken to use smaller than usual sutures and
smaller spacing to minimize bleeding from the anasto­
motic sites. Jackson Pratt drains were left as monitors for
bleeding. These drains proved useful in identifying post­
operative bleeding in one patient.

Immunosuppression was induced intraoperatively with
tacrolimus (Prograf), 0.05 mg/kg over 24 hours in a con­
tinuous intravenous infusion, and methylprednisolone. 1 g.
Maintenance corticosteroid therapy consisted of 20 mg of
methylprednisolone every 24 hours. An intravenous infu­
sion of tacrolimus, 0.05 mg/kg, was continued until gas­
trointestinal function returned.

In the immediate postoperative period, hemody­
namic monitoring and fluid management were per­
formed in the standard way. All blood drawing was limited.
Coagulation was monitored by thromboelastography, pro­
thrombin time, and platelet count. Any fibrinolysis was cor­
rected with e-aminocaproic acid.

Minimal blood drawing guidelines were observed
throughout the hospital stay. All patients again received
erythropoietin and ferrous sulfate Fe 59 until their hemato­
crit levels rose to more than 0.35.

STATISTICAL COMPARISON

Of the 1009 patients undergoing transplantation during the
study period, 445 were adults with UNOS status 3 prior­
ity. We reviewed the charts of these 445 patients, search­
ing for patients who fulfilled our restrictive guidelines. Only
19 of these patients met our guidelines. All 19 patients un­
derwent transsection. The in-hospital charges and the charges
for the use of blood products for all these patients were com­
pared with the charges of the corresponding group of
Jehovah's Witnesses who underwent transplantation. The
Mann-Whitney U test was used for the statistical compari­
on of these charges.

longer, with a resultant mean increase in the hematocrit
level of 0.08. Patient 4 sustained a progressive decrease in
hematocrit level, despite erythropoietin therapy, and platelet­
pheresis was not used due to a low initial platelet count.

Estimates of operative blood loss from inspection, rec­
covery of red blood cells in the cell savers, and sponge
weighting were approximately 250 mL for patient 1, ap­
proximately 700 mL for patient 2, and approximately 750
ML for patients 3 and 4. The mean amount of recovered
and reinfused red blood cells, not including the phleboto­
mized blood for plateletpheresis, was less than 200 mL in
each patient. Patient 1 had no transfusable blood recov­
ered, owing to a small amount of surgical bleeding. The
in-hospital charges of the study patients with UNOS status
3 priority were compared statistically with the charges
of the 19 comparison patients. The difference between
the total in-hospital charges was statistically significant ($P < 0.05$).
The mean amount of blood products transfused for the
comparison group was 8.82 U of packed red blood cells, 7.95
U of fresh frozen plasma, and 6 U of platelet concentrates.
The comparison patients generated 3.8% of their total
charges from the blood bank and the blood products. The
charges for erythropoietin therapy and plateletpheresis were
approximately $3000 for each patient, but none exceeded
this amount. The charges for erythropoietin therapy alone
were $1500 per patient.

COMMENT

No other surgical endeavor requires as much attention to
and expertise with blood conservation techniques as ma­
jor surgical procedures performed on Jehovah's Wit­
esses. Our report illustrates that excellent survival for liver
transplantation can be achieved in these patients. The idea
of performing a liver transplantation without blood is
deemed so uncommon and dangerous that all patients with
religious or even scientific objections to blood transfusion
have not been considered for liver transplantation. How­
ever, the techniques for performing this procedure are avail­
able to us, and we have shown that, with our stepwise, mul­
tidisciplinary approach, this procedure is possible.

The problem presented to us was twofold. One as­
pect was ethical; Jehovah's Witnesses believe that the life force is contained in the blood. This belief has a specific scriptural basis,22,23 and their belief is protected by legal precedent.22,23 Therefore, we as physicians cannot transplant an adult Jehovah's Witness without his or her consent. Parting from that premise, performing a liver transplantation without blood products and with the least amount of danger to the patient was our second major issue. It was clear to us in the beginning that the establishment of informed consent was of prime importance. This principle required us to obtain a state court ruling for patient 4, the minor child of Jehovah's Witness parents, who was in dire need of a liver transplant. The ruling allowed us to do our best to save the child's life, including the use of blood transfusions. Nevertheless, all techniques for blood conservation were used just as with the other three patients, whose operations were done without the safety net of a blood transfusion.

The restrictive guidelines were developed to identify surgical risks for exsanguination. In fact, we have evaluated the cases of 12 patients previously and continue to evaluate cases for this procedure. Two of these patients have died of variceal hemorrhage; eight other cases are at various stages of evaluation.

Preoperative conditioning was of the utmost importance. Patients with liver disease and resultant anemia, from either chronic blood loss or chronic disease, are excellent candidates for erythropoietin therapy.24 Erythropoietin therapy was initiated regardless of the interval between evaluation and transplantation, although 2 weeks is the usual time when erythropoietin starts to show an effect.24 Goodnough et al24 have shown that preoperative erythropoietin can increase the amount of autologous blood in elective orthopedic procedures. Preoperative erythropoietin therapy and the limitation of phlebotomy for laboratory evaluation showed us that this was potentially a major area of improvement, not only in the Jehovah's Witnesses but in all candidates for liver transplantation. Intraoperatively, two

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Table 1. Characteristics of Study Patients

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Patient No.</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
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<tbody>
<tr>
<td>Postnecrotic cirrhosis</td>
<td></td>
<td>3</td>
<td>3</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>Primary biliary cirrhosis</td>
<td></td>
<td>3</td>
<td>3</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>Alpha-1-antitrypsin deficiency</td>
<td></td>
<td>19</td>
<td>19</td>
<td>19</td>
<td>19</td>
</tr>
<tr>
<td>Fulminant hepatic failure</td>
<td></td>
<td>13</td>
<td>13</td>
<td>13</td>
<td>13</td>
</tr>
<tr>
<td>UNOS priority status*</td>
<td></td>
<td>3</td>
<td>3</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Age, y</td>
<td></td>
<td>58</td>
<td>46</td>
<td>19</td>
<td>13</td>
</tr>
<tr>
<td>Previous surgery</td>
<td></td>
<td>None</td>
<td>None</td>
<td>Central splenorenal shunt, cholecystectomy</td>
<td>None</td>
</tr>
<tr>
<td>Immediate indication for orthotopic liver transplantation</td>
<td>Variceal hemorrhage, encephalopathy</td>
<td>Encephalopathy, weakness, vertebral compression fractures</td>
<td>Encephalopathy</td>
<td>Fulminant failure</td>
<td></td>
</tr>
<tr>
<td>Albumin level, g/L</td>
<td></td>
<td>23</td>
<td>30</td>
<td>20</td>
<td>25</td>
</tr>
<tr>
<td>Bilirubin level, µmol/L (mg/dL)</td>
<td></td>
<td>174.4 (10.2)</td>
<td>218.9 (12.8)</td>
<td>6.8 (0.4)</td>
<td>473.7 (27.7)</td>
</tr>
<tr>
<td>Ascites†</td>
<td></td>
<td>++ ++ ++ ++</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grade of encephalopathy‡</td>
<td></td>
<td>2</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
</tbody>
</table>

* UNOS indicates United Network for Organ Sharing. See UNOS Board of Directors.* 1991, for an explanation of UNOS priority status for transplantation.
† Two plus signs indicate requiring medical therapy; three plus signs, requiring aggressive diuretic therapy with large-volume paracentesis.
‡ For encephalopathy grades: 2 indicates alert with diminished level of consciousness; 3, alternating stupor with agitation; and 4, coma.

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Table 2. Analysis of Blood Conservation Therapy

<table>
<thead>
<tr>
<th>Laboratory Values</th>
<th>Patient No.</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4*</th>
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<tr>
<td>Hematocrit level</td>
<td></td>
<td>0.26</td>
<td>0.30</td>
<td>0.32</td>
<td>0.25</td>
</tr>
<tr>
<td>At initial evaluation</td>
<td></td>
<td>0.40</td>
<td>0.39</td>
<td>0.45</td>
<td>0.23</td>
</tr>
<tr>
<td>At transplantation</td>
<td></td>
<td>269 000</td>
<td>204 000</td>
<td>255 000</td>
<td>NA</td>
</tr>
<tr>
<td>Platelet count, ×10^9/L</td>
<td></td>
<td>161 000</td>
<td>111 000</td>
<td>193 000</td>
<td>NA</td>
</tr>
<tr>
<td>Following platelethpheresis</td>
<td></td>
<td>225 000</td>
<td>185 000</td>
<td>202 000</td>
<td>NA</td>
</tr>
<tr>
<td>Postoperatively</td>
<td></td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
</tbody>
</table>

* NA indicates not applicable.
other problems were solved. One was diminishing the loss of red blood cells: the other was correcting coagulopathy. The monitoring and the correction of coagulopathy were the most difficult of these problems. Plateletpheresis allowed us to conserve platelets. Several studies have shown a reduction in the need for blood transfusion, fresh frozen plasma, and platelet concentrates with the use of autologous, platelet-rich plasma in cardiac surgery.2,20 Our transfusions of autologous, platelet-rich plasma contained a mean platelet count of 4.5 x 10^11/L for 300 to 400 mL. According to our blood bank, this amount is equal to 6 to 8 U from random donors. As can be seen in three of the four patients, the drop in the platelet count at the end of the procedure was minimal (Table 2). Again, this technique does not have to be limited to selected patients.

Intraoperative cell salvage has been used extensively in liver transplantation.3,4 Fortunately, the effect of cell salvage in our study patients was underestimated due to minimal bleeding, but the normovolemic hemorrhage may have played an important role in minimizing the loss of red blood cells. The complications sustained by our patients are not uncommon in liver transplantation, yet their relationship to the blood conservation techniques used remains unclear.

In our current medical environment of managed care and ever increasing fiscal concerns, other factors to be considered are the charges generated by the use of blood products. Our study group showed a significant decrease in the total in-hospital charges from the charges of the comparison group. Other centers have studied the charges for cell salvage alone and found a savings of $1800 per patient.6 Our results concur with this finding, and we believe that adding other blood conservation techniques does not add to the expense but rather enables the conservation of blood, which in turn results in the generation of fewer transfusion-related charges.

In conclusion, to perform liver transplantation on Jehovah's Witnesses, we were able to identify several existing techniques for blood conservation that could add a level of efficiency and safety to all liver transplants, and we propose the use of these techniques whenever possible. Whether using these techniques and using less blood products is cost-effective will require further study, perhaps a randomized trial.


Reprint requests to Suite 4C. 3601 Fifth Ave. Pittsburgh PA 15213 (Dr Ramon).

REFERENCES

24. In re Estate of Brooks, 32 Ill 2d 361; 372-373 (Ill App Ct, 1 Dist. 1965).

DISCUSSION

Ingemar Davidson, MD. Dallas. Tex: The authors should be commended for being able to do liver transplants without blood transfusions. I assume that this included FFP and albumin. If one can do this in Jehovah's Witness patients without blood transfusions, shouldn't this be the goal in all liver transplants and, if so, are you currently trying to do that in your routine liver transplants?
My second question is whether or not you have a protocol for intraoperative fluid therapy or replacement therapy in your routine liver transplants. If so, what are the principles? Do you use colloids? Who decides: you surgeons or the anesthesiologists? What would you do if the Jehovah's Witness patient bleeds out of control? How much would you actually save in terms of money per patient if you could transplant without blood transfusions? Please tell us how you resuscitate your clinical single-organ (liver) shock model.

Mohammed Atik, MD, Los Angeles, Calif: The feat to use no blood in three of their four selected liver transplants is indeed impressive; that they could do these complex operations with such a small amount of blood loss is even more remarkable. Obviously their accomplishment is principally due to their operative planning and skill. Credit should also be given to their avoidance of transfusion of stored blood and the perioperative withdrawal and reinfusion of patients' own blood and platelets. There is evidence that multiple transfusion of stored blood and platelet dysfunction augment coagulopathy and bleeding tendencies. It is well known that an important limiting factor, besides hematocrit, for oxygen delivery and tissue perfusion, is the compensatory ability of the heart to increase cardiac output in the face of blood loss. In the absence of cardiovascular dysfunction, a hematocrit of around 35% is optimum in normovolemic patients. Most patients do well with a hematocrit of 30%, and those without cardiovascular and pulmonary disease can tolerate a hematocrit as low as 20% perioperatively, provided their plasma volume is maintained. These principles demonstrated by the authors are also applicable to other areas of surgery.

At UCLA, in 18 consecutive, elective reconstructive operations for aneurysm and occlusive disease, we have used half as much blood transfusions as in comparable operations reported by other well-respected medical centers (mean of 1.7 U vs 4.5 U of blood). More pertinent to this discussion, six of our patients (or in one third of our patients), no blood or platelets, autologous or otherwise, were used, with no ill effects. We could have done better if we did not have unavoidable blood loss (mean of 1000 ± 495 cc) due to use of porous prosthesis, flushing, and heparinization and if we did not deal with older patients (mean age of 64 ± 7 years) with considerable cardiovascular disease and limited cardiac compensatory mechanism to tolerate a low hematocrit. Our experience with these operations, all performed by residents under supervision, though not as spectacular as that of the authors, confirms their findings and demonstrates that complex operations, traditionally performed with several units of blood, can be performed safely with little or no blood transfusions.

Dr Ramos: First of all, Dr Davidson, we were not allowed to use FFP in our patients. only albumin and hetastarch. That is why we included PT greater than 15 in the restrictive guidelines. We are presently undergoing plans for a randomized trial of cell salvage and these techniques in the average liver transplant. Unfortunately we have found a bit of resistance from several of our surgeons, but I think that we will be able to overcome this resistance.

The intraoperative management of fluids is managed by Anesthesia. Dr Kang is a world-class liver transplant anesthesiologist and has published extensively on both cell salvage and on resuscitation and coagulation in liver transplantation. He was the anesthesiologist of record in all of these cases.

The question is, what would we do if the patient starts bleeding uncontrollably? There is only one thing legally we could have done, and that is to pray. The rights of these patients are protected by legal precedent, and we are not allowed to transfuse an adult Jehovah's Witness. If we do, it is assault. Dr Roger Jenkins from Massachusetts has published a paper using cell salvage alone and found a $1800 savings in orthotopic liver transplants in about 40 cases. He didn't transplant Jehovah's Witnesses, but his average blood utilization was approximately 35 U.

We optimize filling pressures by using 4-5 L of crystalloid. The isovolemic hemodilution takes place in actually every liver transplant because these patients have not eaten or drunk fluids for about 24 hours; when they come to the operating room, they are fairly dehydrated. Their hematocrits are high. If we optimize filling pressures with 2-4 L of either albumin or hetastarch or even crystalloid, we can obtain high oxygen transports in these patients who, by virtue of their portal hypertension, already have cardiac outputs that are increased to 8-10 L. We can obtain oxygen transports between 800 mL to 1000 mL per minute. The hematocrit of 35% was chosen arbitrarily by agreement between our departments.

The question about whether this should be used for every liver transplant is exactly why I wrote this paper. I have learned a lot from doing these patients. Unfortunately, since 1991, we haven't found one to fit our restrictive guidelines.