Liver transplantation in a Jehovah's Witness with ankylosing spondylitis

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Purpose: Orthotopic liver transplantation is typically associated with large volume blood loss. Technological and pharmacological advances permit liver transplantation in patients who formerly were not candidates for this surgery because of strict limitations on blood product administration. We describe a liver transplant in a Jehovah's Witness with ankylosing spondylitis.

Clinical features: A 49-yr-old Jehovah's Witness with ankylosing spondylitis and end stage liver disease secondary to sclerosing cholangitis underwent orthotopic liver transplantation. Recombinant human erythropoietin (4,000 IU sc every two days for four weeks, then 4,000 IU sc every week) established a normal hemoglobin concentration preoperatively (>140 $g \cdot L^{-1}$ compared with 120 $g \cdot L^{-1}$ baseline). Intraoperatively, strategies for reducing risk of blood product transfusion included avoidance of hypothermia (T>35°C), minimal blood sampling (four 1 ml samples), normovolemic hemodilution (two units), administration of Aprotinin (2 million units bolus dose followed by infusion of 500,000 $u \cdot hr^{-1}$), and return of blood (1,500 ml) scavenged from the operative field. Estimated blood loss was 2,200 ml. The preoperative and postoperative hemoglobin concentration was 147 $g \cdot L^{-1}$ (hematocrit 0.45) and 123 $g \cdot L^{-1}$ (hematocrit 0.37), respectively. No blood products were required and he was discharged three weeks postoperatively without complication.

Conclusion: Technological and pharmacological advances allow patients to undergo surgery traditionally associated with large volume blood loss with reduced risk of blood product administration.

Objectif : La transplantation du foie orthotopique est typiquement associée à une perte de sang importante. Les progrès technologiques et pharmacologiques permettent de réaliser une transplantation hépatique chez des patients qui n'auraient pu subir cette opération auparavant à cause de limitations rigoureuses d'administration des produits sanguins. Nous décrivons une greffe hépatique chez un témoin de Jéhovah qui présente une spondylarthrite ankylosante.

Éléments cliniques : Un témoin de Jéhovah de 49 ans souffrant de spondylarthrite ankylosante et d'une maladie hépatique terminale secondaire à une cholangite sclérosante a subi une greffe hépatique. L'administration d'érythropoïétine recombinante humaine (4 000 UI sc aux deux jours pendant quatre semaines, puis 4 000 UI sc chaque semaine) a établi une concentration d'hémoglobine préopératoire normale (>140 $g \cdot L^{-1}$ comparée à 120 $g \cdot L^{-1}$ au départ). Les stratégies peropératoires adoptées pour réduire le risque lié à la transfusion de produit sanguin comprenaient l'absence d'hypothermie (T >35 °C), le prélèvement minimal de sang (quatre échantillons de 1 ml), l'hémodilution normovolémique (deux unités), l'administration d'aprotinine (des bolus de deux millions d'unités suivis de perfusion de 500 000 $u \cdot h^{-1}$) et le retour du sang épuré (1 500 ml) provenant du champ opératoire. La perte sanguine a été de 2 200 ml. La concentration préopératoire et postopératoire d'hémoglobine a été de 147 $g \cdot L^{-1}$ (hématocrite 0,45) et 123 $g \cdot L^{-1}$ (hématocrite 0,37), respectivement. Aucun produit sanguin n'a été nécessaire et le patient a quitté l'hôpital trois semaines après l'opération sans complication.

Conclusion : Les progrès technologiques et pharmacologiques permettent de réduire les risques liés à l'administration de produit sanguin et de réaliser des opérations traditionnellement associées à d'importantes pertes sanguines.

THERE are few accounts in the literature of successful orthotopic liver transplantation in Jehovah's Witnesses.[1–4] With refinement of surgical and anesthetic techniques as well as advances in critical care, operative procedures associated with the potential for large volume blood loss are being carried out in this population with decreasing rates of morbidity and mortality. Nevertheless, "bloodless" surgery in this context still presents a formidable challenge to both surgical and anesthetic teams. For this reason, a report is provided of the measures that we employed to help reduce the requirement of blood product transfusion in a Jehovah's Witness undergoing liver transplantation.

Case report

A 49-yr-old 57 kg Caucasian male Jehovah's Witness was referred to the transplant clinic after the recent onset of jaundice and pruritus. His previous medical history included severe ankylosing spondylitis diagnosed at age 20 yr, Crohn's disease diagnosed at age 34 yr, IgA nephropathy and hypertension. The patient had a normal echocardiogram and his ECG showed normal sinus rhythm with left ventricular hypertrophy by voltage criteria. Pulmonary function tests demonstrated an FEV_1 of 2.16 L (73%), FVC of 2.52 L (73%) and FEV_1/FVC of 86 (103%). Endoscopic retrograde cholangiopancreatography demonstrated small calibre intrahepatic and extrahepatic ducts with multiple stenoses compatible with the diagnosis of sclerosing cholangitis. The indication for transplantation was three episodes of cholangitis requiring *iv* antibiotics. The patient also had undergone a previous laparascopic cholecystectomy.

After routine initial pre-transplant investigations were completed, the patient was placed on 300 mg $FeSO_4$ TID *po* and 4,000 IU recombinant human erythropoietin *sc* every two days and was listed for liver transplant. His initial hemoglobin concentration was 120 g·L^{-1}. Once a target hemoglobin of 135 g·L^{-1} was achieved after four weeks, he was maintained on 4,000 IU erythropoietin *sc* every week. His hemoglobin peaked at 154 g·L^{-1} and remained above 140 g·L^{-1} until the time of transplantation. Other medications included sulfasalazine, indomethacin, misoprostol, enalapril, and lansoprazole.

A suitable donor became available seven months after enlistment. On the day of transplant, his hemoglobin was 147 g·L^{-1} (hematocrit 0.45) with a platelet count of 270 x 10^9·L^{-1}. He had a prothrombin time (PT) of 11.4 sec, partial thromboplastin time (PTT) of 31.5 sec, International Normalised Ratio (INR) of 0.928, and fibrinogen concentration of 3.63 g·L^{-1}.

Factors II, V, VII, VIII, IX, X, XI and XII levels were within the normal range. Blood electrolyte values were normal as was the BUN (7.2 mMol·L^{-1}) and creatinine (65 mMol·L^{-1})

Because of the airway difficulties associated with the ankylosing spondylitis, after careful positioning of the head the trachea was intubated with a fibreoptic bronchoscope following adequate sedation (3.0 mg midazolam and 5 μg sufentanil) and airway topicalization (bilateral superior laryngeal nerve block and inhalation of aerosolised lidocaine 4%). General anesthesia was induced with 25 μg sufentanil and 60mg propofol and muscle paralysis was achieved with 10 mg pancuronium. Anesthesia was maintained with isoflurane in an O_2 / air (50%:50%) mixture, and an infusion of 1 mg·hr^{-1} midazolam and 25 μg·hr^{-1} sufentanil. Neuromuscular relaxation was maintained with periodic doses of pancuronium. Monitoring consisted of ECG (leads II & V), pulse oximetry, capnography, nasopharyngeal T°, and a nerve stimulator. Invasive systemic blood pressure was recorded via a catheter inserted into a radial artery, and pulmonary artery and central venous pressures *via* a catheter inserted into an internal jugular vein. The patient's temperature was maintained > 35°C using a water-heated mattress and warmed air delivered to the upper and lower body. All fluids administered through intravenous catheters in the upper extremities (#14 & #16 gauge) were warmed using a Hot Line™.

After induction of anesthesia, the patient was given a bolus of 2 million units Aprotinin followed by an infusion of 500,000 units·hr^{-1} in anticipation of primary fibrinolysis that may arise during the anhepatic and reperfusion phases of liver transplantation.

Normovolemic hemodilution was achieved by removing two units of whole blood (each unit approx 500 ml) from the patient prior to commencement of surgery and storing them into transfusion bags, while infusing a volume of crystalloid in a 3:1 ratio to that removed. The transfusion bags were maintained connected to the patient *via* Continu-Flo® Solution Set tubing connected to the *iv* catheters, in accordance with the wishes of the patient. In keeping with a strategy of blood conservation, minimal blood tests were drawn intraoperatively. Four 1 ml samples of arterial blood were sent for blood gas, hematocrit and electrolyte (calcium & potassium) determination. A baseline hematocrit of 0.45 was recorded shortly after induction of anesthesia. The hematocrit was 0.34 after removal of the first unit and 0.28 after removal of the second unit (approximately 30 and 60 min following induction, respectively). A hematocrit of 0.25 was determined at the end of the anhepatic phase after

four hours following induction. The two units of autologous blood were transfused during the last 60 min of surgery. Blood was scavenged from the operative field, washed and immediately re-transfused using a COBE® BRAT 2 cell saver. In this case, 2,800 ml were scavenged from the surgical field and 1,500 ml of hemoconcentrated blood were returned to the patient. The estimated blood loss combining weight of sponges and cell saver loss was 2,200 ml. A total of 12,000 ml crystalloid (8,000 ml normal saline, 4,000 ml lactated Ringer's) and 500 ml PENTASPAN® were administered intraoperatively, and urine output was approximately 5,000 ml.

Due to size differences between the patient and the transplanted liver as well as intestinal edema, fascial closure was not possible at the end of the operation. A cutaneous closure was completed after six hours of operating time and the patient was brought to the intensive care unit. The immediate postoperative laboratory results were hemoglobin 123 $g \cdot L^{-1}$ (hematocrit 0.37), platelet count $175 \times 10^9 \cdot L^{-1}$, PT 15.3 sec, PTT 67.7 sec, INR 1.702. Postoperative use of blood products was not required. Although the patient's mental and physiological status would have permitted extubation in the immediate postoperative period, owing to the potential difficulties in re-establishing tracheal intubation in the case of deterioration, the trachea was extubated the next day, approximately 20 hr after the operation. He returned to the operating room four days later for fascial closure of the abdominal wall. During the postoperative period, the patient's coagulation parameters rapidly returned to normal and he was discharged from hospital three weeks after transplantation.

Discussion
With increased public awareness concerning the potential complications of transfused blood products, patients may be reluctant to accept blood products even in the face of an increased risk to their health. The medical field has adapted to these concerns by using pharmacological measures to enhance hematopoiesis and coagulation and technological advances to decrease intraoperative blood loss. The successful outcome in the patient described in the present report may be attributed to the preoperative and intraoperative implementation of some of these strategies.

In a case series of four patients with religious objection to blood transfusion who underwent liver transplantation, Ramos and colleagues[1] outlined six criteria that would disqualify patients from a bloodless surgery protocol (Table). The patient in this report would not have been disqualified using these criteria. Such criteria are useful in determining which patients are acceptable risks for surgery assuming that modern techniques of perioperative blood conservation are implemented.

TABLE Restrictive guidelines for bloodless surgery protocol for liver transplantation.[1]

1. Hct < 0.35 after erythropoietin treatment
2. Platelets $< 100,000 \times 10^9 \cdot L^{-1}$.
3. PT > 15.0 sec.
4. Splanchnic venous anatomy that requires extensive vascular reconstruction.
5. Active bleeding
6. Renal failure and other major organ dysfunction (excluding liver)

The preoperative use of recombinant human erythropoietin is becoming more common in anemic patients undergoing surgery with the potential for large volume blood loss.[5-7] Initially used in hemodialysis patients, the restoration of a normal hemoglobin level was shown to decrease anemia-related complications such as left ventricular hypertrophy and congestive heart failure as well as to attenuate the uremia-related bleeding diathesis seen in chronic renal failure patients.[8,9] The preoperative use of recombinant human erythropoietin is a more recent strategy, having received HPB approval for this use in Canada in 1996. Healthy patients can expect a rapid return to baseline hemoglobin levels after the donation autologous blood for retransfusion during elective surgery.[7,10] Anemic patients treated with erythropoietin can expect a return to normal hemoglobin levels.[11] The adverse effects of recombinant human erythropoietin may include a rise in blood pressure and thrombosis of permanently installed venous access devices.[8]

The use of intraoperative and postoperative blood scavenging systems has reduced the amount of allogeneic blood transfusions required by patients. These techniques are, however, expensive and require relatively sophisticated equipment and trained personnel. While a few case reports suggest that DIC, ARDS and renal failure can arise from the reintroduction of fat microemboli, denatured protein, free hemoglobin, cell fragments, and platelet-leukocyte microaggregates into the blood stream,[12,13] more carefully designed studies have failed to show a significant increase in these complications. The washing phase after centrifugation eliminates these products as well as heparin, plasma elastases and soluble cytokines such as TNF-alpha.[13] While coagulation disorders associated with transfusion of a large volume of blood products are well described, it is not

clear to what extent retransfusion of scavenged blood *per se* contributes to a coagulopathy. Traditionally, patients undergoing bowel surgery and cancer resection are not considered as suitable candidates for the use of intraoperative blood scavenging because of the fear of retransfusing bowel flora and exfoliated cancer cells. However, the recent use of blood scavenging techniques in trauma cases with intestinal perforation did not yield more patients with positive blood cultures or wound infections, even though the washing phase does not eliminate all bacteria. Processing of scavenged blood does not eliminate tumour cells thus mandating the use of a special filter if this strategy is to be employed during cancer surgery.[13]

Acute normovolemic hemodilution (ANH) has been advocated as a safe, easy and inexpensive way to avoid exposure to allogeneic blood.[6,12,13] There are several theoretical advantages to this technique:

1. Blood lost in the field has a lower hematocrit and therefore represents a saving in terms of red cell mass loss.
2. Reinfusion of withdrawn blood exposes patients to a large volume of their own platelet and factor-rich blood, thus augmenting hemostasis.
3. Acute normovolemic hemodilution reduces the viscosity of blood and therefore the systemic vascular resistance (SVR). This decrease in SVR increases the cardiac output (CO) without an increase in cardiac work.[12,13]
   Experimental models and clinical studies suggest that the optimum balance between the increase in perfusion as a result of decreasing viscosity and the decrease in oxygen carrying capacity secondary to the decrease in red cell mass occurs at a hematocrit of approximately 30%.[6,12,13] This may help to explain why little clinical benefit has been demonstrated in transfusing patients with a hematocrit > 30% and why mathematical models of ANH have failed to demonstrate any benefit until the patient was bled to a hematocrit < 30%.[14] However, with hematocrits < 30%, patients with coronary and carotid stenoses may not be able to increase flow to the heart and brain leading to ischemic complications.
4. Acute normovolemic hemodilution is performed in anesthetized, paralysed and ventilated patients in whom oxygen consumption is diminished, thereby improving the margin of safety in decreasing the delivery of oxygen by removing blood.[12,13] A recent meta-analysis of prospective, randomised, controlled studies of ANH concluded that this technique reduces the likelihood of exposure to allogenic blood and the volume of blood transfused.[15] Nevertheless, there appeared to be marked heterogeneity of the results and the benefit of ANH cannot at present be definitively supported.[15] The potential benefits of ANH, as outlined above, prompted its use in the present case.

Aprotinin has been demonstrated to decrease the risk of allogenic blood transfusion in a recent meta-analysis of prospective, randomised, controlled studies of pharmacological strategies to decrease bleeding associated with cardiac surgery.[16] A similar analysis has not been done with patients who have undergone liver transplantation. Although there is evidence to support the use of aprotinin in this type of patient,[17] the usefulness of this approach has been challenged.[18] Interestingly, the benefits conferred by aprotinin using high doses, as employed in this case, may also be achieved with somewhat lower doses.[19]

Repeated blood sampling for laboratory analysis should not be underestimated as a source of blood loss, and such analysis was kept to a minimum in this case. The avoidance of severe hypothermia prevented temperature-related coagulopathy. Although venovenous bypass has been suggested to decrease blood product requirements[3] this technique is almost never used at our institution during liver transplantation and we elected not to use it in this patient, particularly since he had a normally functioning heart. Often left unreported in discussions of perioperative blood conservation is meticulous surgical technique. Dissection was done almost exclusively with electrocautery, as emphasised in previous reports.[3] There are new surgical devices to minimise blood loss which are described in a recent review.[20]

A most important contributor to the successful clinical outcome in this case is that the patient received his liver transplant before he demonstrated severe liver failure. Thus, the patient's liver was able to maintain normal blood concentrations of factors necessary for hemostasis. Patients that require bloodless liver transplantation have to be listed for surgery early before their coagulation profile is severely affected.

Finally, the value of discussion and preoperative involvement of a multidisciplinary team cannot be overstated. Clarification of the patient's wishes, concerns and beliefs concerning transfusion of blood products is critical. In this particular case, the potential legal, ethical and medical complications of performing a liver transplant in a patient refusing transfusion of blood products were discussed at many multidisciplinary rounds involving anesthesia, surgery, hematology and intensive care personnel. Specific consultation was obtained with the hospital medical ethicist and lawyer

and from the Canadian Medical Protective Association (CMPA). Following several frank discussions with the patient and his family, the patient's decision concerning the potential use of blood products in the face of a life-threatening situation was carefully documented.

In conclusion, we describe a Jehovah's Witness patient with ankylosing spondylitis who underwent liver transplantation without requiring transfusion of blood products during the perioperative period. The pharmacological and technological strategies employed to help conserve blood in the perioperative period, as described in this report, may help to reduce the necessity for the transfusion of blood.

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