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Living donor liver transplantation without the use of blood products

不使用血產品的活體肝移植

We report on two patients who presented with unresectable hepatocellular carcinoma complicating hepatitis B liver cirrhosis. After evaluation, both patients were accepted for liver transplantation. Being aware of the scarce availability of cadaveric liver grafts and the long waiting time, family members volunteered to be donors for the two patients. Living donor liver transplantation using right lobe liver grafts, including the middle hepatic vein, was subsequently performed without the use of blood products in both the donors and recipients. All involved recovered uneventfully from their respective operations.

本文報導兩名患有無法手術切除肝細胞肝癌合併發乙型肝炎肝硬化的病人。經評估後，兩名病人均獲安排肝移植。由於屍肝供應短缺及輪候時間漫長，其家人自願決定成為供體。我們為受體進行右半肝連肝中靜脈活體肝移植，供體及受體手術均無需輸注血液製品。所有供體及受體在手術後均順利康復。

Introduction

Orthotopic liver transplantation (OLT) is typically associated with a large volume of blood loss, although transfusion requirements have gradually decreased with refinements in surgical and anaesthetic techniques. There are even a few reports in the literature of successful liver transplantation without transfusion of red cells in Jehovah's witnesses.[1] In recent years, living donor liver transplantation (LDLT) using right lobe liver grafts has been frequently employed, especially in countries where there is scarce or no supply of cadaveric liver grafts. However, LDLT can be technically demanding in both the donor and recipient operations. We report two cases in which successful LDLT using right lobe liver grafts was performed without the use of blood products in both the donors and recipients.

Case reports

Case 1

A 51-year-old Chinese man had a history of chronic hepatitis B–related liver cirrhosis and splenectomy for thrombocytopaenia in 1995. He also had a history of left lateral segmentectomy for a 2 cm hepatocellular carcinoma (HCC) in 1998. Histological examination of the resected specimen showed a 2 cm HCC with lymphovascular permeation (TNM stage II disease). The postoperative course was complicated by a single episode of gastrointestinal bleeding from oesophageal varices, which was controlled by injection sclerotherapy. Thereafter, he was maintained on oral propranolol.

Two years after hepatic resection, a 7 cm HCC recurrence was detected in the right lobe of the liver on computed tomography (CT). The patient's clinical condition was explained in detail to his family members who, after discussing the effectiveness and limitations of various treatment options, including local ablative therapy, regional chemoembolisation, and liver transplantation, opted for the latter. After evaluation, the patient was put on the transplant recipient waiting list. Being aware of the scarce availability of cadaveric liver grafts and a long waiting time of more than 2 years, the patient's wife, aged 44 years, volunteered

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to be a liver donor. The patient's family members were not solicited for liver donation, and the decision to undertake LDLT was based entirely on the wife's voluntary intent. An independent psychological assessment performed by a clinical psychologist confirmed that her decision to donate was made without coercion. Both the husband and wife were informed of the possible morbidity and mortality of the donor and recipient operations. Donor evaluations, including blood biochemistry, CT with volumetric measurement, and hepatic angiography, confirmed that the wife was indeed suitable to be a liver donor.[2,3] At the time of the operation, laboratory studies of the recipient showed a platelet count of 67 x 10^9/L (normal range, 150-450 x 10^9/L), a haemoglobin level of 145 g/L (normal range, 140-175 g/L), an albumin level of 30 g/L (normal range, 35-50 g/L), a bilirubin level of 15 μmol/L (normal range, 5-21 μmol/L), an aspartate aminotransferase level of 128 U/L (normal range, 20-48 U/L), an alanine aminotransferase level of 105 U/L (normal range, 10-40 U/L), an alphafoetoprotein (AFP) level of 43 ng/mL (normal range, 0-20 ng/mL), and a prothrombin time of 12.8 seconds (normal range, 10-13 seconds).

The donor operation began with a bilateral subcostal incision with upward midline extension. Operative cholangiography was performed with fluoroscopy to outline the biliary anatomy. The right hepatic artery and right portal vein were isolated at the liver hilum. Parenchymal transection was performed to the left of the middle hepatic vein using an ultrasonic dissector without portal vascular inflow clamping. When the recipient's total hepatectomy was complete, the donor's right lobe liver graft, together with the middle hepatic vein, was harvested and back table perfusion with University of Wisconsin solution started. The intra-operative blood loss was 500 mL and the donor did not require any blood product transfusion. Her postoperative course was uneventful and she was discharged home on the seventh day after the operation.

The recipient operation also began with a bilateral subcostal incision with upward midline extension. Marked adhesion relating to two previous upper abdominal operations was encountered. Total hepatectomy was performed with preservation of the hepatic arterial branches, left and right portal veins, and stumps of the hepatic veins. However, intra-operative cell salvage was not employed because of the presence of malignancy. The liver graft was implanted to the orthotopic position, with hepatic venous anastomoses of the right hepatic and middle hepatic veins being followed by right portal vein anastomosis. The graft began functioning immediately on reperfusion, as evidenced by bile production, and was soft in consistency. Hepatic arterial anastomosis was performed using microvascular techniques. Doppler ultrasound showed patency and normal pulsatile waveforms in the hepatic venous anastomoses. Roux-en-Y hepatico-jejunostomy was constructed to the right hepatic duct. The intra-operative blood loss was 800 mL and the total fluid replacement was 3500 mL. The recipient remained haemodynamically stable throughout the operation and did not require any blood product transfusion. His postoperative immunosuppressive therapy consisted of steroids and tacrolimus. He was also put on oral lamivudine for hepatitis B prophylaxis. He was extubated on postoperative day 1, resumed a hospital diet on postoperative day 2, and was discharged home on postoperative day 17. Pathological examination of the liver explant confirmed the preoperative radiological diagnosis and showed macronodular cirrhosis of the liver, with a 7 cm moderately differentiated HCC.

Case 2

A 49-year-old Chinese man was attending the surgical clinic for the management of multifocal HCC complicating hepatitis B–related liver cirrhosis. He had been a known hepatitis B carrier since 1995 and had a slightly raised AFP level of 26 ng/mL. Computed tomography demonstrated three foci of HCC inside a cirrhotic liver, the largest one being 2.5 cm in diameter. Regional chemoembolisation was given once. However, unsatisfactory treatment was evident on subsequent CT, which demonstrated incomplete lipiodol staining and growing tumours. The patient's clinical condition was explained in detail to his family members who, after discussing treatment options, which included continuation of regional chemoembolisation and liver transplantation, opted for transplantation. After evaluation, the patient was put on the transplant recipient waiting list. Being informed of the scarce availability of cadaveric liver grafts and a long waiting time of more than 2 years, the patient's son, aged 22 years, volunteered to be a liver donor. The family members were not solicited for liver donation, and the decision to undertake LDLT was based solely on the son's voluntary intent. An independent psychological assessment performed by a clinical psychologist confirmed that his decision to donate was made without coercion. Both the father and son were informed of the possible morbidity and mortality of the donor and recipient operations. Donor evaluations, including blood biochemistry, CT with volumetric measurement, and hepatic angiography, confirmed that the son was indeed suitable to be the liver donor. At the time of the operation, laboratory studies of the recipient father showed a platelet count of 234 x 10^9/L, a haemoglobin level of 132 g/L, an albumin level of 32 g/L, a bilirubin level of 13 μmol/L, an aspartate aminotransferase level of 34 U/L, an alanine aminotransferase level of 45 U/L, an AFP level of 7 ng/mL, and a prothrombin time of 12.3 seconds.

The donor operative procedure was essentially the same as that reported in the case 1 donor. The intra-operative blood loss was 250 mL and the donor did not require any blood product transfusion. His postoperative course was uneventful and he was discharged home on the sixth day after the operation.

The recipient operative procedure was also essentially the same as that reported in the case 1 recipient. Again,

immediate graft function was noted. The intra-operative blood loss was 1300 mL and the total fluid replacement was 7500 mL. The recipient remained haemodynamically stable throughout the operation and did not require any blood product transfusion. His postoperative immunosuppressive therapy also consisted of steroids and tacrolimus. He was also put on oral lamivudine for hepatits B prophylaxis. He too was extubated on postoperative day 1, resumed a hospital diet on postoperative day 2, and was discharged home on postoperative day 17. Pathological examination of the liver explant confirmed the preoperative radiological diagnosis and showed liver cirrhosis, with three foci of moderately differentiated HCC.

Discussion

Following its introduction more than a decade ago, LDLT has significantly eased the crisis of donor organ shortage for liver transplantation. First performed successfully in children,[4-6] application of this innovative technique has recently been extended to adults through the use of a right lobe graft.[7,8] It is now the main source of liver grafts in areas where there is scarce or no supply of cadaveric grafts.

Donor safety is of prime importance during LDLT.[9] In particular, minimising blood loss during donor hepatectomy minimises the risk of postoperative morbidity due to hepatic dysfunction, as well as the risk of transmittable disease due to contaminated blood product transfusion. Since the establishment of the liver transplant programme in our institution in 1991, hepatectomy has been performed for 90 donors. To date, none has required any blood product transfusion, with the exception of a single patient who had anaemia from thalassaemia and received one unit of homologous blood transfusion.

Orthotopic liver transplantation is typically associated with a large volume of blood loss. Bontempo et al[10] reported a median red cell transfusion requirement of 10 units in an unselected liver transplant population. Fortunately, increased understanding of coagulopathy and fibrinolysis,[11] together with improvements in surgical haemostasis using argon beam coagulation and the introduction of intra-operative cell salvage, have led to a reduced demand for blood product transfusion.[12] However, cell salvage is expensive and requires relatively sophisticated equipment and trained personnel to perform. Theoretically, disseminated intravascular coagulation, adult respiratory distress syndrome, and renal failure can arise from the reintroduction of fat microemboli, denatured protein, free haemoglobin, cell fragments, and platelet-leukocyte microaggregates into the blood stream, although better designed studies have so far failed to show a significant increase in these complications.[13] Unfortunately, both our transplant recipients had HCC and hence were not considered suitable candidates for cell salvage because of fears of retransfusing exfoliated cancer cells.

The timing of the procedure is particularly crucial. Because of the infrequent supply of cadaveric grafts at our centre, patients put on the waiting list have to wait at least 2 years before they can have a transplant. It is our experience that more than half of these candidates succumb to major complications before a timely graft is available. In addition, even if a transplant does eventually take place, the operation can be difficult because of extensive vascular adhesions that have arisen as a result of repeated episodes of spontaneous bacterial peritonitis occurring in the interim. Both our patients had HCC and, given their clinical conditions, it did not seem appropriate to wait for cadaveric grafts to become available. Living donor liver transplantation, however, enabled early transplantation to take place, before decompensation of liver function and associated coagulopathy had occurred, thus allowing the operations to be done successfully without the use of blood products.

In a recent meta-analysis of prospective, randomised, controlled studies of pharmacological strategies designed to decrease bleeding associated with cardiac surgery, administration of aprotinin decreased the risk of allogenic blood transfusion.[14] The use of aprotinin to decrease transfusion requirements in patients undergoing OLT is supported by the results of a recent multicentre, randomised study,[15] although the effectiveness of this approach has been challenged.[16] Aprotinin is not routinely given to patients undergoing liver transplantation at our centre, and was not given to either of the two recipients reported here.

Meticulous surgical technique and haemostasis with electrocautery and argon beam coagulation contributed significantly to the avoidance of blood transfusion in the two recipients described here. Maintaining haemostasis was particularly important, since both patients had HCC and one had a history of two previous upper abdominal surgeries. Another major contributory factor was our increasing experience with, and refinement of, the LDLT technique using right lobe liver grafts.[17] We placed great emphasis on careful reconstruction of the right and middle hepatic vein anastomoses, so that liver graft dysfunction and congestion would not occur. Liver graft congestion increases bleeding from the cut surface of liver and the hepatoduodenal area due to unresolved portal hypertension. Excessive blood loss during liver transplantation can result in unfavourable outcomes, including cerebrovascular complications.[18] Furthermore, perioperative transfusion has been found to promote recurrence of HCC after hepatic resection and result in shorter disease-free and overall survival.[19,20] Avoidance of blood product transfusion will thus be one of our aims in future liver transplant operations.

Liver transplantation is a recognised treatment for HCC in selected patients, and the survival results of those chosen to undergo OLT for HCC are not inferior to those undergoing OLT for non-malignant disease. Mazzaferro et al[21] reported excellent disease-free and overall survival rates of 92% and 85%, respectively, 4 years after OLT in 35

patients with a solitary HCC not exceeding 5 cm in diameter or no more than three tumours, with none greater than 3 cm in diameter. To justify the use of scarce cadaveric liver grafts in this population, many transplant centres have employed the Mazzaferro criteria to select candidates for OLT. However, the same selection criteria should not be strictly applied to patients undergoing LDLT, as the grafts are 'dedicated to the beloved' of the donors. Moreover, because the recipients of LDLT are not competing with other recipients for cadaveric grafts,[22] the survival results of LDLT for HCC should be compared to those in the absence of transplantation in any attempt to justify the technique. In fact, the Mazzaferro criteria have been questioned in recent studies, and expanding the tumour size limits does not seem to have adversely affected survival rates. Yao et al,[23] for example, reported excellent survival results of 90% and 75.2% at 1 and 5 years, respectively, in patients undergoing OLT for HCC ≤ 8 cm in size.

Although LDLT can be performed without the use of blood products in selected patients, this does not imply that it can or should be recommended for all patients with HCC. The efficacies and drawbacks of treatment options available should be discussed with potential donors and recipients, and ethical issues should be adequately addressed. Of paramount importance is a proper psychological assessment of the donor to assure appropriate voluntarism on their part. This informed consent must be gained before establishing the suitability of their liver for transplantation through the usual functional and radiological tests.

Conclusion

Living donor liver transplantation without the use of blood products still poses a major challenge, but can be achieved in selected patients, including those with HCC, provided the surgical technique and perioperative care are of a sufficiently high standard, and a timely graft is available.

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