



Liver transplantation in Jehovah's Witnesses -two cases report-

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Liver transplantation is especially challenging in patients who are Jehovah's Witnesses because their religious beliefs prohibit the receipt of blood products. We present two cases of living donor liver transplantation performed in adult Jehovah's Witnesses in South Korea without the use of blood products. In the first case, preoperative erythropoiesis-stimulation therapy increased hemoglobin levels from 8.1 to 13.1 g/dl after 9 weeks. In the second case, hemoglobin levels increased from 7.4 to 10.8 g/dl after 6 months of erythropoiesis-stimulation therapy. With the combination of acute normovolemic hemodilution, intraoperative cell salvage, and use of transfusion alternatives, liver transplantation was successfully performed without transfusion of blood products.

Key Words: Bloodless medical and surgical procedures, Jehovah's Witnesses, Liver transplantation, Operative blood salvage.

Liver transplantation (LT) is associated with significant blood loss and often requires significant transfusions. With the advancement of surgical and anesthetic techniques and concurrent understanding of the hemostatic system of end-stage liver disease [1], the incidence of massive bleeding and the need for transfusion have dramatically decreased over the last decade. LT in Jehovah's Witnesses (JW) is especially challenging as their religious beliefs prohibit the acceptance of blood products, which

often complicates medical and surgical treatment [2]. Although the likelihood of massive bleeding is reduced in modern LT surgery, there is still a chance of unexpected bleeding that may necessitate transfusions. We report two cases of living donor LT (LDLT) in adult JW patients at two hospitals without the administration of blood products.

Case Reports

Case 1

A 54-year-old female JW patient (body weight, 50 kg) diagnosed with liver cirrhosis complicated by hepatitis B viral infection presented to the bloodless center in our institute to assess whether LDLT was possible. She had massive ascites without encephalopathy, but was in good physical condition otherwise. Initial laboratory findings were hemoglobin (Hb) of 8.1 g/dl, platelets $51 \times 10^9/L$, prothrombin time (PT) 1.65 (international normalized ratio, INR), albumin 2.1 g/dl, creatinine 1.5 mg/dl, and total bilirubin 3.04 mg/dl. We discussed with a surgeon the possibility of LT without transfusion. Acceptable transfusion

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alternatives were confirmed after discussion with the Jehovah's Witnesses Hospital Liaison Committee and the patient. The patient refused to receive any red blood cells (RBCs), fresh frozen plasma, or platelet concentrate, but agreed to receive human albumin, recombinant factor VIIa and VIIIa, fibrinogen concentrate, cryoprecipitate, and intraoperative cell salvage (ICS) via a continuous circuit to the patient's circulation. She also accepted reinfusion of collected whole blood acquired from acute normovolemic hemodilution (ANH) provided via a continuous circuit. The organ transplantation ethics committee then met to decide whether those surgical restrictions were ethically acceptable because this was the first LT in an adult JW patient in South Korea. Following committee approval, the patient decided to undergo LT. Her son, who is not a JW, chose to donate his right hepatic lobe.

Erythropoiesis-stimulating agent (ESA) therapy with recombinant human erythropoietin (rHuEpo) and intravenous iron was initiated along with folic acid and vitamin B12 to increase the patient's red cell mass. Subcutaneous rHuEpo (Epokine[®], CJ HealthCare, Seoul, Korea) at 10,000 IU and intravenous iron (Venoferrum[®], JW Pharmaceutical, Seoul, Korea) at 200 mg were administered three times per week. After 9 weeks' administration, the Hb level increased to 13.1 g/dl and the patient was scheduled for surgery the next day. On arrival at the operating theater, monitoring was initiated with a five-lead ECG, noninvasive blood pressure cuff, pulse oximeter, and bispectral index sensor. Anesthesia was induced with propofol at 80 mg and, after the administration of rocuronium at 50 mg, the patient was intubated. Anesthesia was maintained with oxygen, air, desflurane, and continuous remifentanyl and rocuronium infusion.

Hemodynamic monitoring included the right radial and femoral artery pressures, central and right femoral vein pressures, pulmonary artery and capillary wedge pressures, and cardiac output measurements via a Swan-Ganz catheter. A transesophageal echocardiography probe was inserted to monitor volume status and systolic function and to diagnose the cause of any sustained hypotension that occurred during surgery. The right radial artery was used for blood sampling and drainage of the patient's blood for ANH. After vascular catheterization, ANH was initiated. The patient's blood volume was estimated at 3,000 ml (60 ml/body weight, kg). The target Hb level was approximately 10.0 g/dl. We collected 960 ml of whole blood for ANH, which was divided into three CPDA-transfusion bags (320 ml each), while maintaining continuous infusion to the patient via the radial artery catheter. Briefly, we did not replace blood loss with fluid simultaneously as is usually done in ANH. No fluid was administered until after collection of the first 500 ml whole blood to prevent dilution of RBC, coagulation factors, and platelets. Thereafter, 750 ml 5% Albumin[®] (Green Cross Corp., Yongin, Korea) and 500 ml Plasma Solution A[®] (CJ HealthCare,

Seoul, Korea) were administered to replace lost blood until ANH was completed. It took 15 min to obtain each unit. There were no changes in mean arterial pressure, heart rate, mixed venous oxygen saturation (SvO₂, maintained around 90%), or cardiac output during 45 min of ANH. Central venous pressure (CVP) decreased by 1 mmHg from the initial value of 4 mmHg. Pre-ANH Hb was 13.4 g/dl, platelets $32 \times 10^9/L$, and fibrinogen 113 mg/dl. Post-ANH Hb was 10.8 g/dl, platelets $29 \times 10^9/L$, and fibrinogen 82 mg/dl. To prevent fibrinolysis, 40 mg/kg tranexamic acid was administered intravenously for 20 min before the surgical incision and then continuously infused at a rate of 10 mg/kg/h. All blood from the surgical field was salvaged using a cell saver until biliary anastomosis was initiated. Plasma Solution A[®] was administered at a rate of 5 ml/kg/h during the surgery. Blood loss was replaced with Plasma Solution A[®] at a 1 : 3 ratio throughout the surgery unless there was sudden blood loss, which was replaced by 5% Albumin[®] at a 1 : 1 ratio. CVP was maintained at less than 5 mmHg throughout the dissection phase. Norepinephrine (0.1 to 0.27 $\mu\text{g}/\text{kg}/\text{min}$) was used as a primary vasopressor to maintain the mean arterial pressure at 65 mmHg or above. During the pre-anhepatic phase, approximately 7,300 ml ascitic fluid was drained. Acute hemorrhage occurred when the inferior vena cava was injured during mobilization of the diseased liver, which caused 350 ml of blood loss until prompt hemostasis using a total inferior vena cava (IVC) clamp. We began to transfuse salvaged blood approximately 1 h after starting surgery to maintain the hemoglobin level at around 9 g/dl. One hour after beginning the anhepatic phase, ANH blood was retransfused slowly from the recently collected blood, as is recommended within 6 h of collection. The Hb level was maintained above 9 g/dl until the end of the surgery. Fibrinogen decreased to 56 mg/dl 3 h postoperatively. Fibrinogen concentrate (Fibrinogen Inj[®], Green Cross Corp., Yongin, Korea) at 3.0 g was administered intravenously, which increased the fibrinogen concentration to 136 mg/dl.

There was no fibrinolysis on thromboelastography or oozing in the surgical field during the operation. Graft reperfusion was accomplished without any cardiovascular instability. SvO₂ remained high during the entire operation, suggesting that there was no global oxygen supply/demand imbalance. The operation concluded uneventfully and the patient was transferred to the intensive care unit (ICU) while intubated. The total anesthesia duration was 8 h and the operation time was 6.6 h. Total blood loss was 940 ml. Plasma Solution A[®] at 4,800 ml, 5% Albumin[®] at 1,000 ml, and 470 ml of salvaged blood were administered. Urine output was around 900 ml.

Postoperatively, Hb was 11.9 g/dl, platelets $19 \times 10^9/L$, PT 2.49 INR, and fibrinogen 122 mg/dl (Table 1). The postoperative recovery was uneventful and the patient did not receive any blood products. She was discharged on postoperative day 15 without

Table 1. Hematologic and Coagulation Profiles, Mixed Venous Oxygen Saturation, Kaolin-activated Thromboelastography Findings and Re-infusion of Salvaged Blood during Surgery

	Baseline		Pre-anhepatic phase		Anhepatic phase			Postreperfusion phase		End of operation
	Before ANH	After ANH	1 h	2 h	5 min	1 h	80 min	10 min	2 h	
Hemoglobin (g/dl)	13.4	10.8	9.5	8.5	9.5	9.2	9.1	9.0	11.4	11.9
Platelets ($\times 10^9/L$)	32	29		42	41		38	33	33	19
INR	1.72	1.92	2.31		2.81		3.0	3.24	2.38	2.49
Fibrinogen (mg/dl)	113	82	62		56		136	127	119	122
SvO ₂ (%)	93	90	92	89	90	89	92	92	94	94
R (min)	11.6		10.1		10.3		10.8	9.9	6.6	20.1
K (min)	20.4		-		9.9		6.4	4.2	8.5	12.2
Alpha angle (degree)	18		17.2		27.6		33.4	44.7	26.7	17.6
MA (mm)	20.7		18.7		28.9		31.4	40.6	28.5	34.8
LY30 (%)	0		0		0		0	0	0	0
Cell salvage transfusion (ml)				213		135			122	
ANH blood transfusion (ml)						320		320		320

ANH: acute normovolemic hemodilution, INR: international normalized ratio, SvO₂: mixed venous oxygen saturation, R: reaction time, time from the start of the sample run to the first detectable clot formation (amplitude = 2 mm), K: time from R to the clot amplitude of 20 mm (to specify the kinetics of the clot development), Alpha angle: the angle formed by the slope between the amplitude of the trace at 2 mm and 20 mm, MA: maximum clot amplitude, LY 30: level of fibrinolysis at 30 after MA was reached.

any complications. She is still in good health 5 years after surgery.

Case 2

A 47-year-old male JW patient suffering from alcoholic liver cirrhosis presented for LDLT. He had diabetes that was controlled with insulin and was administered ESA therapy with rHuEpo, which increased his hematocrit in preparation for bloodless surgery. After 27 episodes of ESA therapy over the six months before LDLT, the Hb level increased from 7.4 to 10.8 g/dl. Preoperative evaluations (echocardiography, pulmonary function test, esophagoduodenoscopy, chest radiography, and electrocardiogram) were within normal limits. Laboratory tests revealed Hb of 10.8 g/dl, platelets $46 \times 10^9/L$, PT 1.84 INR, fibrinogen 159 mg/dl, and albumin 3.2 g/dl.

Anesthesia was induced with pentothal sodium at 400 mg, and after administration of vecuronium at 10 mg, the patient was intubated. Anesthesia was maintained with oxygen, air, and sevoflurane. Hemodynamic monitoring included the right radial and femoral artery pressures, central and right femoral vein pressures, pulmonary artery and capillary wedge pressures, and cardiac output measurements via a Swan-Ganz catheter. Despite insertion of the Swan-Ganz catheter, cardiac output was not checked, so we monitored only SvO₂. To maintain the body temperature during surgery, fluid was heated with a Level 1[®] Fast Flow Fluid Warmer (Smiths Industries, Rockland, MA, USA) and peripheral vascular access was blocked to prevent infusion of cold fluids.

During the intraoperative period, vecuronium was infused continuously (1.0 µg/kg/min) and sevoflurane was replaced with isoflurane after positioning the retractor. We regulated the concentration of isoflurane while aiming for 40 to 60 on the bispectral index. During the pre-anhepatic phase, there were no ascites and 500 ml of Hextend[®] (CJ HealthCare) was infused. We used regular insulin because the patient's glucose was 219 mg/dl and dopamine (5.0 µg/kg/min) was administered continuously for hemodynamic stability. Arterial blood gas analysis was performed every 1 h to monitor the Hb level. The authors administered 300 ml salvaged blood whenever the Hb level dropped below 9 g/dl. The lowest Hb level was 6.7 g/dl during the anhepatic phase. Continuous infusion of norepinephrine (0.05 µg/kg/min) was started before reperfusion and tranexamic acid at 500 mg was injected twice during the anhepatic and postreperfusion phase. There was no evidence of fibrinolysis on thromboelastometry, which was monitored at least every 2 h during surgery. To reduce blood loss, we used ICS except during biliary opening until the end of surgery. To conserve fluid effectively, we wrung out the gauze pads prior to removing them from the abdominal cavity.

During the 12 h and 30 min of surgical time, 8,300 ml Plasma Solution A[®], 2,050 ml 5% Albumin[®], 900 ml half normal saline, 1,000 ml Hextend[®], and 2,065 ml of salvaged blood were infused. Urine output was 570 ml and estimated blood loss was about 2,500 ml. After surgery, the patient was transferred to the ICU while still intubated with continuation of dopamine (5 µg/kg/min) and norepinephrine (0.2 µg/kg/min).

Table 2. Hematologic and Coagulation Profiles, Mixed Venous Oxygen Saturation, and Re-infusion of Salvaged Blood during Surgery

	Baseline	Pre-anhepatic phase		Anhepatic phase			Postreperfusion phase					End of operation
		1 h	2 h	Start	1 h	2 h	5 min	30 min	1 h	2 h	3 h	
Hemoglobin (g/dl)	10.0	9.9	8.0	8.4	6.7	8.2	9.1	9.2	7.8	9.7	8.3	10.5
Platelets ($\times 10^9/L$)	38		36	38	26		35		43			39
INR	2.15		2.65	2.79	3.45		5.0		6.22			7.75
Fibrinogen (mg/dl)	161		132	118	96		71		57			49
SvO ₂ (%)	89	90	90	94	86	96	97	93	91	92	90	90
Cell salvage transfusion (ml)				300		600	400		300		465	

INR: international normalized ratio, SvO₂: mixed venous oxygen saturation.

The last blood test before the end of anesthesia revealed Hb of 10.5 g/dl, platelets $39 \times 10^9/L$, PT 7.75 INR, and fibrinogen 49 mg/dl (Table 2). The patient was extubated on the first postoperative day. Although he could not receive a transfusion of fresh frozen plasma or cryoprecipitate, PT was decreased and fibrinogen was increased with 2.18 INR and 211 mg/dl, respectively about 7 days after LDLT.

On postoperative day 17, leakage of the hepaticojejunostomy and small bowel perforation were suspected, so the patient underwent a second operation for resection and anastomosis of the small bowel. Continuous renal replacement therapy was initiated and maintained until postoperative day 28. He was transferred to the ward 36 days after LDLT, but was reintubated and transferred to the ICU on postoperative day 60 due to hypotension and respiratory failure. He died on postoperative day 76 due to several complications including intra-abdominal infection, pneumonia, and chronic renal failure.

Discussion

Blood transfusions during LT have decreased dramatically during the last decade owing to the advancement of surgical and anesthetic techniques. Nonetheless, this surgery is still likely to necessitate transfusions due to associated blood loss, the incidence of which varies widely among transplantation centers. JWs refuse to accept transfusions due to their religious beliefs, which present a challenge to the surgical team. LT in JW patients has been successfully performed in the United States [3,4] and Europe [5,6]. Reports consistently suggest that successful LT in JW patients requires a judicious combination of careful patient selection, preoperative optimization of RBC quantity, intraoperative blood conservation strategies (ANH and ICS), use of transfusion alternatives, and adaptive anesthetic techniques.

With regard to patient selection, although no universal selection criteria exist to select the most ideal LT candidates who are JW patients, a minimum preoperative hematocrit of 35% is consistently required among reports [3,6]. The most important

aspect of preoperative preparation of a LT recipient is to increase red blood cells to a safe level to account for blood loss. Additionally, the initial Hb value was the only biochemical variable linked to RBC transfusions in 700 consecutive LT patients [7]. This is usually achieved with ESA therapy consisting of rHuEpo and iron therapy. In previous reports, the dose of rHuEpo in JW LT patients varied among institutions, ranging from 10,000 to 40,000 IU/wk [3,4]. Response to therapy usually occurs within 1–2 weeks. In the current cases, it took 9–24 weeks of ESA therapy to restore the Hb level sufficiently to proceed with surgery.

Implementation of intraoperative blood conservation strategies is also important to achieve transfusion-free surgery. ANH and ICS are acceptable for most JW patients during surgery and are therefore widely used. In the first case, the authors were able to collect about 1 L of whole blood using ANH. Notably, we did not administer fluids until we had collected 500 ml of whole blood to acquire coagulation factors and platelets as well as undiluted RBCs. Our technique differs slightly from the conventional ANH technique in which an equivalent volume of colloid or crystalloid is infused simultaneously to maintain normovolemia [8]. Fortunately, the patient did not develop hypotension or tachycardia during this period.

In both cases, ICS was used to conserve blood in the surgical field. This technique has been reported to conserve 2.1 g/dl of Hb per patient or two RBC unit transfusions for LT operation [9]. We retransfused 470 ml and 2,065 ml of salvaged blood, respectively, in our two cases. Again, this is relevant to save two to five units of RBCs.

In both cases, the Hb level was regarded as the indicator of the need for salvaged blood retransfusion (ICS and ANH blood) to maintain the Hb level at around 9 g/dl. Some advocate for using physiologic monitors such as SvO₂ and cerebral oximetry to evaluate global and regional perfusion [10]. This can compensate for the intermittent nature of Hb measurement, which may not detect acute changes in global or regional oxygenation during the operation. Thus, continuous SvO₂ monitoring may be helpful to assess the need for re-infusion of salvaged blood.

However, in the current case report, SvO₂ remained high during the various phases of LT (sudden or protracted blood loss), even when the Hb level decreased to 6.7 g/dl. A consistent SvO₂ can result from sufficient supply and decreased oxygen demand during anesthesia.

Replacement of coagulation factors as well as RBC is also challenging because JW patients will not accept fresh frozen plasma or platelets. Alternatives to coagulation factor replacement are therefore important. In contrast to the second case, the patient in the first case agreed to receive cryoprecipitate. This was possible because acceptance of cryoprecipitate depends on the patient's free will, apart from church doctrine. However, we administered fibrinogen concentrate in place of cryoprecipitate because of potential advantages such as decreased immunogenic and infectious complications, as well as rapid availability because fibrinogen concentrate does not need to be thawed [11]. Fibrinogen is the first coagulation factor to decrease when blood loss occurs with subsequent volume replacement [11]. Replacing fibrinogen can support fibrin clotting even without transfusion of platelets. Fibrinogen concentrate contains pure fibrinogen, making fibrinogen levels after administration predictable. In the first case, 3.0 g of fibrinogen concentrate increased the level by 80 mg/dl, from 56 mg/dl to 136 mg/dl. It has been reported that administration of 1 g of fibrinogen concentrate increases the fibrinogen level by 25 mg/dl [12], which is consistent with the first case.

Antifibrinolytic therapy has also been shown to decrease the incidence and amount of transfusion when used when used in LT. In both cases, we used tranexamic acid to achieve this goal. It is controversial whether antifibrinolytic agents are re-

lated to thrombotic events. A single center study reported that all patients who developed intracardiac thrombosis had not received antifibrinolytics, suggesting that antifibrinolytics do not predispose to intracardiac thrombosis [13]. Others advocate that routine administration of antifibrinolytics is not indicated because of the low incidence and successful treatment of hyperfibrinolysis in patients who are bleeding and showing signs of hyperfibrinolysis on thromboelastography [14]. As there is no consensus regarding the routine use of antifibrinolytics for LT in JW patients, the authors used this agent to reduce blood loss while risking thrombosis.

In the first case, we restricted fluids with concomitant use of a low CVP. We kept the CVP close to 5 mmHg during the pre-anhepatic and anhepatic phases. This was achieved by administering 5 ml/kg/h of crystalloids and occasional colloids according to the quantity of blood lost. A recent randomized controlled trial that evaluated the effect of a low CVP during the pre-anhepatic and anhepatic phases revealed that this strategy significantly decreased blood loss [15].

In summary, LDLT in JW patients can be successfully performed in carefully selected patients by using preoperative RBC augmentation, intraoperative blood conservation techniques such as ANH and ICS, transfusion alternatives and antifibrinolytics, and anesthetic protocols that reduce intraoperative blood loss.

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