

## Research Article



# Retrospective review of bloodless liver transplant recipients at a single center

## Abstract

**Introduction:** Jehovah's Witness (JW) patients are known to refuse blood transfusions, but may accept solid organ transplants. Liver transplantation (LT), with the possibility of substantive blood loss, is more challenging in patients who refuse blood transfusion. In this report, we present a case series of JW patients who underwent LT at our center over the past two decades and discuss their management and outcomes.

**Methods:** We retrospectively reviewed the medical records of JW patients who underwent LT at our institution from 1994 through 2015.

**Results:** Nine JW patients underwent LT and were included in the study. The median age of the group is 42.38 years old (range 35–56), with seven females and two males. No patient received blood products during or after LT. During the first three post-operative months, five patients suffered acute rejection episodes, three developed systemic sepsis, two developed acute kidney injury, and seven survived the first year post-LT.

**Conclusion:** LT is feasible without blood transfusion. The one-year mortality rate in JW patients is comparable to LT recipients who received blood transfusion at our center. With a multidisciplinary protocol and better surgical techniques, it is possible to perform LT without the use of blood products, which can result in favorable postoperative outcomes.

**Keywords:** Jehovah's witnesses, bloodless liver transplantation, patient outcomes

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**Abbreviations:** LT, liver transplantation; JW, jehovah's witness; TEG, thromboelastography; MELD, model for end-stage liver disease; TEE, Transesophageal Echocardiogram; PRS, post-reperfusion syndrome; AKI, acute kidney injury

## Introduction

Liver transplantation (LT) is among the most technically challenging surgeries, with an estimated cost ranging from \$410,000 to \$730,000 per procedure.<sup>1</sup> Given the likelihood of blood product transfusion due to surgical blood loss, Jehovah's Witness (JW) patients are still excluded from LT in many transplantation centers due to their refusal of blood products on the basis of religious beliefs. Our institute has performed LTs for JW patients since 1990 and our first four patient series by Starzl et al.<sup>2</sup> Since that case series, bloodless LT has been demonstrated to be feasible with acceptable patient outcomes in many centers throughout the world. Also, the resultant focus on utilization of blood conservation strategies has shown that standard-of-care transfusion of blood products is associated with worse post-LT outcomes, including higher risk of infection, longer hospitalizations, and more long-term allograft complications.<sup>3–5</sup> Here, we present our follow-up single center experience with JW patients undergoing bloodless orthotopic LT over 20 years.

## Methods

This retrospective medical record review was approved by our local Institutional Review Board (IRB protocol #13070351). All JW LT recipients from the period of January 1994 through December 2015 were included in the study. We collected preoperative, intraoperative, and postoperative data. Preoperative data included demographic information, Model for End-stage Liver Disease (MELD) score, Child-Pugh score, etiology of liver failure, and pre-transplant laboratory

test results. Intraoperative data included hemodynamic data, volume and type of fluid replacement, and requirement for inotropic support. Postoperative data included length of ICU and hospital stay, incidence of post-LT acute kidney injury (AKI) and sepsis, and one-year patient and graft survival.

## Results

All data are presented as mean  $\pm$  SD or median and range. The results of our review of the medical records are summarized as follows:

### Patient characteristics

Between 1994 and 2015, deceased donor LT was performed in nine JW patients, two males and seven females with a median age of 42.38 years of age (range 35–56 years old). Etiology of liver failure was primary sclerosing cholangitis in 44% (four patients), primary biliary cirrhosis in 33% (three patients), and autoimmune hepatitis in 22% (two patients). The mean  $\pm$  SD MELD score was 19.22 $\pm$ 5.9; 70% (seven patients) had a Child-Pugh score of B and 20% (two patients) had a Child-Pugh score of C. None had renal impairment or cardiopulmonary co-morbidities.

### Preoperative management and preoperative data

Baseline preoperative hematocrit was 35.8 $\pm$ 6.78, INR was 1.29 $\pm$ 0.27, platelet count was 115.9 $\pm$ 47.33, and serum creatinine was 0.9 $\pm$ 0.5mg/dL. All JW patients were optimized for LT following strict selection criteria as previously described.<sup>2</sup> Hematocrit was optimized pre-LT with iron, multivitamin supplements, and recombinant erythropoietin (epoetin alfa). Platelet count ranging from 70,000–100,000 was used as one of the selection criteria. All JW patients who received LT agreed to the use of cell-saver salvage blood and human albumin solution. Portal hypertension in these patients was

pharmacologically managed (beta blockers and diuretics) and/or with transjugular intrahepatic portosystemic shunt procedure to minimize gastro-intestinal bleeding complications.

### Intraoperative management and intraoperative data

All patients underwent orthotopic cadaveric LTs, which were performed by the most experienced surgeon on the team using a piggyback surgical technique with veno-venous bypass. Surgical technique included meticulous hemostasis with argon beam diathermy and application of biological hemostats such as fibrin glues and sealants. All patients received general anesthesia with invasive monitoring that included two arterial lines (radial and femoral), a pulmonary artery oximetry catheter with continuous cardiac output measurement, and a 9 FG cannula that is usually inserted in the internal jugular vein for volume resuscitation and connected to a rapid infuser pump. Another 18 FG cannula is inserted in the right internal jugular vein and used as the return conduit for blood from the femoral and portal veins during the veno-venous bypass procedure. Thromboelastography (TEG) is used as the standard of care during LT to monitor coagulation and to detect any fibrinolysis that occurs during the anhepatic or reperfusion phase. Transesophageal echocardiography (TEE) became the standard of care at our transplant center in 2000 and all LT recipients from 2000 to present had TEE as a part of required monitoring. Post-reperfusion syndrome (PRS) was reported in all nine patients and was graded as mild. PRS is defined according to our institutional practice guidelines based on our accepted clinical practice. PRS is considered mild when there is a short-lived decrease in blood pressure and/or heart rate (30%-50% from the pre-perfusion level) that responds to calcium chloride (1gm IV) and/or epinephrine boluses IV (no more than 100 micrograms). Significant PRS is defined as sustained low systemic blood pressure (30%-50% of the pre-perfusion level) that does not respond to boluses of vasopressors and requires continuous vasopressor infusion during the intra-operative and post-operative periods.<sup>6</sup> All nine patients received antifibrinolytic ( $\epsilon$ -aminocaproic acid 250mg IV), which was administered to treat fibrinolysis detected by TEG. All patients received 5% albumin and salvaged cell-saver blood (mean of  $340 \pm 120$ mL), and none received allogeneic blood product transfusion. To minimize blood loss by reducing hepatic and abdominal venous congestion, low CVP (<10cm H<sub>2</sub>O)<sup>7,8</sup> and low intrathoracic pressure were maintained throughout the surgery. Normothermia was maintained and acid-base balance was strictly controlled in all cases. The normovolemic hemodilution technique that is commonly used as a method of blood conservation was not utilized in our group.

### Postoperative outcomes

The mean hematocrit immediately post-LT was  $26.6 \pm 10.8$ , with a nadir of 8-10 points lower than baseline reached by postoperative day 7 and normalized by postoperative day 21 after intensive treatment with iron supplements and epoetin alfa. The average duration of mechanical ventilation was 48.3 hours (range 26.7-73.50hours). The median duration of hospitalization was 15.2 days (range 10.3-34.5) and the median ICU length of stay was 11.55 days (range 4.5-20.5).

### Survival analysis

Although our sample size is very small to conduct a proper survival analysis or to perform propensity-match statistical analysis, it is fair to say that one-year graft and patient survival were comparable to the non-JW LT population at our institution. The first year patient survival was 78%; one patient died within the first month post-LT due to intra-abdominal sepsis, portal vein perforation, and AKI, requiring

renal replacement therapy, and another patient died of sepsis during the second month post-LT.

### Morbidity

AKI within 72 hours post-LT was 22% (two of nine patients) versus an institutional incidence of 52% in non-JW LT.<sup>9</sup> Five patients developed mild episodes of biopsy-proven acute rejection within 90 days post-LT, which was treated with titration of immunosuppression medications. Two patients developed complicated systemic sepsis, three suffered mild wound infection, and two developed aspiration pneumonia.

### Discussion

Our follow-up report of our 20-year of experience with LT for JW patients without homologous blood transfusion and with only albumin and salvaged autologous blood demonstrates the feasibility of bloodless LT. The one-year patient survival (78%) is similar to non-JW LT and comparable to the published data on non-JW LT (83%).<sup>10</sup> LT without transfusion is feasible and the transplantation literature suggests that bloodless strategies may reduce the risk of adverse outcomes, including death. A study of 804 non-JW LT recipients by Cywinski et al.<sup>11</sup> suggested that large volume blood product transfusions are strongly associated with increased mortality and morbidity, although the study failed to establish a single causal relationship between outcomes and blood transfusion. The authors explained that the increase in mortality due to massive transfusion is complex and even likely varies between transplantation centers. Importantly, an emerging and developing focus is examining the influence of anemia and its treatment on overall survival for patients undergoing a variety of surgeries. A study of over 3,000 patients who underwent orthopedic procedures showed that preoperative anemia, perioperative bleeding, or red blood cell transfusion were independent risk factors for increased long-term morbidity and mortality.<sup>12</sup> The early successes of the JW bloodless procedures paved the way for the current investigations of targeted transfusions that are beginning to change our way of thinking about the utilization of blood products.

Given the feasibility of performing bloodless LT in the optimized JW population, it would be useful to identify reliable predictors of those at the highest risk for excessive hemorrhage that could result in a massive transfusion. Cywinski et al.<sup>13</sup> examined these factors and determined that low platelet count and increased MELD score suggest an overall increased bleeding risk in the LT population. Surgical technique and baseline coagulopathy are also implicated in other studies. These reports confirm that multiple valid factors predict massive hemorrhage and could aid in patient selection or perioperative planning. While there is a wide range of variability in blood conserving strategies among bloodless LT centers, the specifics strategies do not appear to strongly influence outcomes, provided that there is careful patient selection, an effective blood augmentation strategy, and meticulous intraoperative blood sparing through surgical technique. It remains clear that these three tenets-strict patient screening, adequate preoperative management, and meticulous surgical expertise-remain essential for the ongoing safety of bloodless LT patients.

Our institution's morbidity data supports the bloodless literature that suggests the notion that less or no blood transfusion will lead to better and improved outcomes in LT recipients or/and when blood administration is more selectively utilized. As previously published, our institutional rate of AKI within 72 hours in non-JW LT<sup>9</sup> recipients was 52%, while it was 22% in our group of JW LT recipients. One of the risk factors for post-LT AKI in the non-JW LT group that was

investigated in this study<sup>9</sup> was transfusion of fresh frozen plasma, which points to the role of blood transfusion in post-LT patient and graft outcomes.

A study by Liu et al.<sup>14</sup> demonstrated that liver allograft complications appeared to be influenced by the use of non-red blood cell blood products such as cryoprecipitate. In a retrospective study of 356 primary LT recipients by Liu et al.<sup>14</sup> intraoperative cryoprecipitate administration was independently associated with an increased risk of post-operative biliary complications. The authors observed increased pathological microthrombus formation and cholestasis in liver biopsies and postulated that it was an immunologically-mediated rejection due to cryoprecipitate. In the absence of clear surgery-related biliary complications, cryoprecipitate (and platelet use) were implicated as risk factors for prolonged severe intrahepatic cholestasis.<sup>15</sup> In another study, Ozkardesler et al.<sup>5</sup> demonstrated that bacteremia and sepsis in the first month following LT were higher in patients who received blood products.

Although there are still considerable risks in performing bloodless LT, the bloodless experience has created a paradigm shift. This setting has allowed conservation of blood product transfusions through an enhanced focus on the dynamic and complex re-equilibration of the hemostatic system during and following LT. There is less solitary reliance on historical markers of coagulation, such as INR, that may have limited validity in the perioperative LT population. The use of real time and point-of-care tests such as thromboelastography<sup>16,17</sup> permits more emphasis on qualitative measures of functionality of the hematologic system. TEG allows an accurate diagnosis and treatment of fibrinolysis that can lead to excessive blood loss.<sup>18,19</sup> More precise treatment of hemostatic derangements is possible due to improved characterization of the changing coagulation profile. Although considerable variability remains between bloodless LT techniques and settings,<sup>20,21</sup> the morbidity and mortality benefits of blood conservation strategies continue to emerge.

## Conclusion

Bloodless LT in JW patients continues to lead to good outcomes with a multidisciplinary team approach and has shifted the emphasis to the importance of the dynamic hemostatic system in the LT population. Avoidance of blood transfusions reduces adverse outcomes known to be associated with transfusions such as post-surgical infections, and has also been shown to improve recuperation time, decrease graft malfunction, permit more rapid re-equilibration of the hemostatic system, and possibly even decrease AKI. Strategies to reduce blood loss have been developed along the continuum of patient care to optimize the therapeutic benefit of LT, including preoperative patient counseling and management, intraoperative blood recovery and bloodless surgical techniques, and more efficient post-surgical laboratory monitoring. Our follow-up review of our 20-year experience once again demonstrates the feasibility of bloodless LT in JW patients. Improved outcomes from these bloodless procedures suggest that there may be value in continuing efforts to selectively extend blood conservation principles to non-JW patients undergoing LT.

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## Conflicts of interest

The authors declare there are no conflicts of interest.

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