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Expanding Living Donor Liver Transplantation: Report of First United States Living Donor Liver Transplant Chain

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Abstract

Living donor liver transplantation (LDLT) enjoys widespread use in Asia, but remains limited to a handful of centers in North America and comprises only 5% of liver transplants performed in the United States. In contrast, living donor kidney transplantation is used frequently in the United States, and has evolved to commonly include paired exchanges, particularly for ABO-incompatible pairs. Liver paired exchange (LPE) has been utilized in Asia, and was recently reported in Canada; here we report the first LPE performed in the United States, and the first LPE to be performed on consecutive days. The LPE performed at our institution was initiated by a non-directed donor who enabled the exchange for an ABO-incompatible pair, and the final recipient was selected from our deceased donor waitlist. The exchange was performed over the course of two consecutive days, and relied on the use and compliance of a bridge donor. Here, we show that LPE is feasible at centers with significant LDLT experience and affords an opportunity to expand LDLT in cases of ABO incompatibility or when non-directed donors arise. To our knowledge, this represents the first exchange of its kind in the United States.

Introduction

Living donor liver transplantation (LDLT) remains the primary method of liver transplantation in Asia but continues to comprise less than 5% of liver transplants performed annually in the United States [1]. As of 2019, only 10 United States transplant centers performed more than 10 LDLT per year [2].

Our center is located in Region 5, and our median Model for End Stage Liver Disease (MELD) score at transplant is 32. Over the past 5 years, we have performed an average of 27 adult to adult LDLT per year in an effort to expand LDLT and enable transplantation in liver waitlist candidates who have a living donor and may otherwise spend a significant amount of time on the waitlist. In 2017, we performed a sentinel living donor liver-kidney exchange [3]. Here, we report our experience with a LDLT chain. Liver paired exchange (LPE) has been

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reported in Asia [4] and Canada [5]; this represents the first report of its kind in the United States.

Case Report

The LPE was facilitated by a female donor who stepped forward to be a non-directed donor. The pair that was assisted were an ABO-incompatible mother (recipient) and daughter (donor). The final recipient in the chain was on our deceased donor liver transplant waitlist. The timing of the procedures is outlined in Figure 1.

All adult to adult living donor hepatectomies at our institution are performed by a single, senior transplant surgeon. Pre-operative cross-sectional imaging is utilized to delineate vascular and biliary anatomy. For right donor hepatectomies, the operation is performed via a bilateral subcostal incision. Post-operatively, the donors are extubated and observed in the intensive care unit (ICU) for one night. Pain control is multimodal and often includes locoregional blocks.

At our institution, the LDLT recipient hepatectomy is performed by the surgeon on liver transplant call, and the LDLT recipient sew ins are performed by a single, senior transplant surgeon. Post-operatively, the recipients are transferred to the ICU. Immunosuppression is steroid-sparing. All recipients are maintained on an octreotide drip for the first 5 days post-operatively and undergo serial graft ultrasounds on PODs1, 3, and 5.

Donor 1

This donor was a 57 year old, otherwise healthy woman who approached our center with the intention of becoming an anonymous, non-directed donor. In addition to the standard donor work-up which includes an assessment by a licensed social worker and a meeting with our Independent Living Donor Advocate, all non-directed donors at our institution are also automatically evaluated by psychiatry. Donor 1 was blood type O negative and had suitable anatomy and liver mass for right lobe donation. Her social work evaluation revealed a history of situational depression, and psychiatry evaluation deemed her to be a suitable donor candidate with appropriate understanding of the donation process and depression symptoms in remission. Donor 1 subsequently underwent right hepatectomy (middle-vein sparing) and cholecystectomy on the same day as Recipient 1; graft mass was 800g. Her intraoperative and post-operative courses were uneventful, and she was discharged home on post-operative day (POD) four after meeting appropriate pain control, nutritional, and functional milestones.

Recipient 1

This recipient was a 71 year old woman, blood type O positive, with a history of cirrhosis secondary to Hepatitis C Virus who had previously achieved sustained virologic response. Her liver disease was complicated by ascites, esophageal varices with a history of bleeding that ultimately required placement of a transjugular intrahepatic portosystemic shunt, hepatic encephalopathy, and prior portal vein thrombosis. She underwent orthotopic living donor liver transplant on the same day as Donor 1 and received the 800g graft. Her post-operative course was notable for a cut edge bile leak, for which she underwent ERCP with stent

placement on POD6, IR drain exchange on POD11, and repeat ERCP with stent exchange and sphincterotomy on POD14. She was ultimately discharged home on POD18.

Donor 2

This donor was a 40 year old healthy woman, blood type A positive, who had initially stepped forward to be a living donor for her mother, Recipient 1. At the outset of the evaluation process, ABO incompatibility was discovered, at which time Donor 2 expressed interest in being considered for an internal swap. Almost one year later, she agreed to participate in this LPE. The day after the Donor 1/Recipient 1 exchange, Donor 2 underwent right middle vein-sparing donor hepatectomy and cholecystectomy, yielding a graft of 550g which was 70% of the predicted volume based on pre-donation cross-sectional imaging. She recovered well post-operatively and was discharged home on POD5.

Recipient 2

The selection process for this recipient began by examining blood type compatible patients listed for liver transplant at our institution to identify potential recipients in whom the donor graft volume (as measured by CT scan) to standard liver volume was more than 40%. We then looked for patients who had a need for transplant that was significant but not well served by our MELD based allocation system. We then selected the patient with the highest MELD score. The decision process was ultimately reviewed and approved by our recipient selection committee. The chosen recipient was a 55 year old woman, blood type A positive, with a history of cirrhosis secondary to primary sclerosing cholangitis complicated by hepatic encephalopathy, a history of spontaneous bacterial peritonitis, and ascites requiring weekly paracenteses. She underwent orthotopic living donor liver transplant on the same day as Donor 2 and received the 550g graft. The graft was notable for a large accessory vein draining segment 6 (6mm) and a large intraparenchymal branch draining segment 5 (7mm). The segment 6 accessory vein was anastomosed in an end to side fashion to the inferior vena cava; the segment 5 vein was extended using a third party iliac vein and also anastomosed in an end to side fashion to the inferior vena cava. Following completion of the vascular anastomoses, the portal vein flow was 2.5 L/minute and the hepatic artery flow was 25 to 30 cc/minute with a sharp upstroke on the waveform but markedly decreased diastolic flow; as a result, the splenic artery was ligated. This decreased portal flow by 500cc/min and increased hepatic artery flow by 20cc/min. POD1 ultrasound demonstrated a continued high resistance waveform in the hepatic artery, so the patient subsequently underwent visceral arteriogram on POD1 which demonstrated patent vasculature. The patient was considered to be at risk for small for size syndrome so a beta-blocker was added to the octreotide, initially esmolol and then transitioned to propranolol. The patient demonstrated some features of small for size with high peritoneal drain output, and hyperbilirubinemia peaking at 10 mg/dl on POD 7 and then decreasing to 4.8 mg/dl by POD11. She was discharged home on POD8.

Discussion

While LPE has been reported in Asia [4] and, more recently, in Canada [5], to our knowledge this is the first LPE to be successfully performed in the United States. In this particular case, the LPE was possible because of a non-directed donor who adamantly wished to maintain

anonymity, an ABO-incompatible donor and recipient pair, and a patient on the deceased donor waitlist. This case highlights the feasibility of LPE at an experienced institution, but also raises three important ethical considerations: 1) utilization of grafts from non-directed liver donors, 2) final recipient selection, and 3) timing of the exchange.

The utilization of grafts from non-directed living liver donors warrants special attention. Between 1998-2018 in the United States, a total of 105 non-directed living donor liver transplants were reported, with the number per year increasing annually [6]. Because of this small number, much remains unknown about the long-term physical, psychosocial, and economic outcomes of these donors. As previously established, following right hepatectomy, donor mortality is estimated to be 0.5% with a morbidity rate of 20% [7,8], but these numbers derive from a population dominated by directed donors, and their generalizability to non-directed donors is certainly unclear. In the assessment of the non-directed living donor, it is particularly paramount to establish that the donor understands these risks, has reasonable and appropriate motivation for donation, and is not under any form of coercion; psychosocial assessment and an honest conversation regarding risks, benefits, and our genuine limitations in understanding quality of life after live donation are essential. Similarly, in the context of LPE, it is critical that the donor from the ABO incompatible pair is comfortable pursuing donation. Some authors have suggested that donors from ABO incompatible pairs participating in LPE, particularly living related donors, should be more thoroughly evaluated to rule out coercion since they cannot use ABO incompatibility as a reason to no longer pursue donation [5,9,10]. Our non-directed donor, as well as the other members of the LPE, felt strongly about maintaining anonymity through the exchange process. A recent study examined the safety and feasibility of anonymous living liver donation [11]; the cohort of 50 anonymous living liver donors included in this study was predominantly white, half female, highly educated, had a prior history of altruistic acts, and the majority learned of the need for living liver donors through social media. Through two years of post-donation follow up, the authors reported excellent outcomes, and postulated that the responsible nature, conscientiousness, and low narcissism of non-directed donors inherently predicted a low risk of regret or dissatisfaction after donation [11].

A second consideration in LPE initiated by a non-directed donor is the selection of the final recipient in the chain. Others have suggested that pediatric waitlist candidates or those candidates whose severity of liver disease is poorly reflected by the MELD score should receive prioritization in these circumstances. In the case of our final recipient, our program considered three elements in the selection process: 1) ABO compatibility, 2) appropriate size match, 3) severity of disease and under-representation in the MELD-based system. Ultimately this recipient was reviewed by our liver transplant selection committee, which is a multidisciplinary group consisting of surgeons, hepatologists, and social workers that reviews all potential liver candidates.

Finally, the timing of the swap is important. Other centers reporting LPE have performed the donor and recipient operations in four operating rooms simultaneously [4,5] which can be logistically challenging, but addresses concerns regarding simultaneity and equalizing risk. In our case, we performed the operations on sequential days. In doing so, we accepted the risk that, given a good outcome in Recipient 1 on the first day, Donor 2 (the “bridge” donor)

might opt out of living donation at the last moment. Re-appropriating terminology from the kidney paired exchange (KPE) literature, a bridge donor is defined as someone who donates more than one day after their intended recipient received a transplant [12]. A recent paper discussing the feasibility of LPE in the United States emphasized that, in the early days of KPE, there was concern that the bridge donor might back out at the last minute and break the chain [13]. As a result, kidney donor operations were initially attempted simultaneously. However, a 2018 review of 344 KPE chains between 2008 and 2016 revealed that only 5.6% of bridge donors broke the chain and the majority of these donors developed a medical issue during their time as a bridge donor that prohibited them from completing donation [12]. Ultimately, because this occurrence was so infrequent, the authors concluded that simultaneous donor operating rooms for chains are unnecessary and may actually deter potential donors based on logistical issues. To our knowledge, there is no literature on staged LPE for LDLT, and therefore our ability to contextualize this practice relies solely on extrapolation from the KPE experience. In our LPE, the operation for Donor 2 began approximately 10 hours after Recipient 1 had received a successful transplant, and while this does not exactly qualify as a bridge donor, Donor 2 could have declined her operation at the last minute. LPE remains in its infancy in North America, but the issue of simultaneity and bridge donors is something that will need to be examined in the liver population specifically as this practice grows.

Conclusion

While LPE is relatively common in Asia, it is just emerging in North America. LPE is feasible at centers with significant LDLT experience and affords an opportunity to expand LDLT in cases of ABO incompatibility, inadequate graft volumes, or when non-directed donors arise. Special considerations should be taken to ensure donor safety and understanding, preserve anonymity, and emphasize bridge donor compliance, when necessary.

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Data Availability Statement

Data sharing not applicable to this article as no datasets were generated or analyzed during the current study

Abbreviations

ICU	intensive care unit
KPE	kidney paired exchange
LPE	liver paired exchange
LDLT	living donor liver transplant

MELD	Model for End Stage Liver Disease
POD	post-operative day

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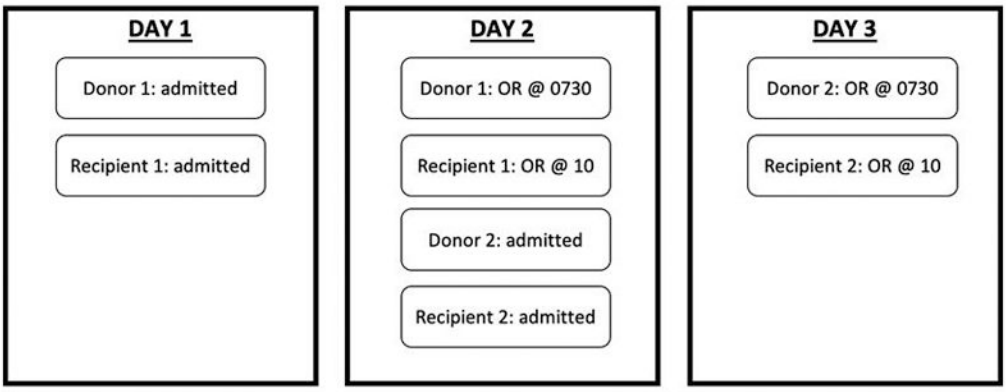

Figure 1:
Logistical timing of liver paired exchange.