Title: Perioperative Management of Living Donor Liver Transplantation: Part 2 – Donors

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Abstract:

Living donor liver transplantation was first developed to mitigate the limited access to deceased donor organs in Asia in the 1990s. This alternative liver transplantation method has become a widely practiced and established transplantation option for adult patients suffering with end-stage liver disease, and it has successfully helped address the shortage of deceased donors. The Society for the Advancement of Transplant Anesthesia and the Korean Society of Transplantation Anesthesiologists jointly reviewed published studies on the perioperative management of adult live liver donors undergoing donor hemi-hepatectomy. The goal of the review is to offer transplant anesthesiologists and critical care physicians a comprehensive overview of the perioperative management of adult live donors. We featured the current status, donor selection process, outcomes and complications, surgical procedure, anesthetic management, Enhanced Recovery After Surgery protocols, avoidance of blood transfusion, and considerations for emergency donation. Recent surgical advances, including laparoscopic donor hemi-hepatectomy and robotic laparoscopic donor surgery, are also addressed.

Keywords: review, liver transplantation, donor, living donor liver transplantation, anesthesia, SATA, KSTA

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Introduction

Part one of the adult live donor liver transplantation (LDLT) review focused on recipient management. This second part focuses on donor perioperative management. These

reviews are the product of a joint effort by members of the Society for the Advancement of Transplant Anesthesia and the Korean Society of Transplantation Anesthesiologists. Featured topics include the current status, donor selection process, outcomes and complications, surgical procedure, anesthetic management, Enhanced Recovery After Surgery protocols, avoidance of blood transfusion, and considerations for an emergency donation. Recent surgical progress, including laparoscopic donor hemi-hepatectomy and robotic laparoscopic donor surgery, is also addressed along with anesthetic management. This review does not include the practice guideline or recommendation given the paucity of the evidence in each domain. Rather, the series intend to serve as an introductory review of the donor management in LDLT.

Donor Selection Criteria, Ethical Considerations, and Processes (Table 1)

LDLT donation from a person without a medical condition necessitating surgery places the donor in a potentially life-threatening situation for the benefit of the recipient alone. Therefore, donor safety must be the primary concern in donor selection (1). To ensure the safety of donors, most centers utilize strict protocols during the donor selection process and accept only the most suitable candidates. Risks to the donor can be mitigated when an experienced transplant team performs the surgery at a high-volume center (2). The selection process is rigorous for directed (recipient known to the donor) and non-directed (often termed “altruistic” or “anonymous”) donations. Donor candidates undergo a staged selection process over many weeks carried out by representatives from the various transplant program teams. This process aims to secure a donor graft while simultaneously protecting the donor candidate, who must be judged by all parties as "competent" to decide to donate and not acting under any coercive, financial, or other pressures. Informed consent must be obtained

for all procedures performed during the evaluation, and the morbidity and mortality risks associated with the procedure itself must be fully explained.

Once contacted by a donor candidate, the transplant coordinator performs a general health screening (age, obesity, medical and surgical history, ABO compatibility) before assessing the donation's social, financial, and psychological impacts on the potential donor. This process includes contact with an independent donor advocate (3) whose role is to provide unbiased information and psychological support to the candidate, and with individuals who have served as LDLT donors and can share their own medical and psychological experiences.

The multidisciplinary transplant team performs further medical evaluations to assess cardio-pulmonary and hepatic risk factors. First-line testing, including chest X-ray, electrocardiography, transthoracic echocardiography, ultrasound, and blood chemistry. Especially, evaluation of the donor's coagulation dysfunction is crucial, including Factor V Leiden mutation, assessment of Protein C and S levels, and antithrombin III levels. Invasive tests may be performed if abnormal results necessitate further investigation (pulmonary function tests, cardiac stress testing with or without catheterization). There is an equal concern for both the graft and the remnant liver of the donor candidate. To assure donor safety and proper graft function in the recipient, estimation of graft volume and detailed anatomic review of the vascular and biliary structures are mandatory. The surgical team's evaluation is focused on assessing the donor's liver anatomy (lobar structure, vascular and biliary networking) using multiple imaging modalities (computer tomography, magnetic resonance imaging, angiography, and cholangiography) to plan the acquisition of an adequately sized graft with suitable anastomosis potential. A liver biopsy is occasionally performed to look for excessive (>10%) steatosis. Donor age and graft steatosis can affect graft function. For donor candidates over 35 years old, less than 15% of fatty changes and

more than 35% of remnant liver volume are recommended for donor right hemi-hepatectomy (4). Only 40% of potential donor candidates are reported as being acceptable for donation (5).

The anesthesiology team performs its preoperative assessment with help from data collected by the transplant coordinator and hepatology and surgical teams. A plan for perioperative care, including postoperative pain management, is communicated to the donor, and consent for anesthesia is obtained before the planned surgical date to allow a "cooling off" period. The potential donor can change their mind and withdraw from the donor process at any time.

Donor Outcomes and Complications

Liver Regeneration and Functional Recovery

Both donor liver regeneration and functional recovery after donation are substantial in the first three to six months after donation hepatectomy. Hepatic blood flow increases during regeneration, with alterations of the portal circulation. The regeneration rate is related to donor remnant volume. Donors with the smallest remnant/total liver volume ratios had larger than expected growth but higher postoperative bilirubin and international normalized ratio at seven and 30 days (6,7). Most laboratory values return to normal ranges within three months, but platelet counts are significantly and persistently lower at every check-up for up to three years post-donation (8). Tracking long-term donor outcomes is essential, but complete follow-up usually diminishes beyond the first year after donation (9).

Morbidity and Mortality

Surgery-related morbidity of living donors reportedly ranges from 16% to 78.3% (10). According to a worldwide survey, the average donor morbidity rate was 24%, with five donors (0.04%) requiring transplantation. The donor mortality rate was 0.2% (23/11,553) and the incidence of near-miss events such as massive bleeding or respiratory failure was 1.1% (11). The most recent Annual Data Report of the Organ Procurement & Transplantation Network/Scientific Registry of Transplant Recipients showed a 10.5% readmission rate for LRLT donors who donated between 2014-2018 at six months and 12.5% at 12 months (12). Reported complications among LRLT donors who donated between 2015-2019 included biliary complications (2.8%), vascular complications requiring intervention (0.8%), re-operation (2.0%), and other complications requiring intervention (6.2%). Of these same donors, 1.0%, 1.5%, and 0.4% experienced Clavien Grade 1, Clavien Grade 2, and Clavien Grade 3 complications, respectively (12).

The Adult-to-Adult Living Donor Liver Transplantation Cohort Study (A2ALL)

Notably, a longitudinal national study on donor outcomes after LDLT donation was initiated in the US. The Adult-to-Adult Living Donor Liver Transplantation Cohort Study (A2ALL) and the A2ALL-2 studies provided robust data from nine liver transplant centers collected between 1998-2014. Principal study purposes included investigating the impact of liver donation on the donor's health-related quality of life (HRQOL), recording donor complications and grading them using the Clavien scale, and understanding pain management and pain control following partial donor hepatectomy. Numerous subsequently powered retrospective and prospective studies have led to critical publications on donor outcomes and complications.

Surgical Complications

In the A2ALL studies, donor complications after donation in 1998-2003 involved 21% of patients, with only 2% being graded as life-threatening and 0.8% leading to death, with 13/405 (3.2%) donor procedures aborted (13). Common complications included bacterial infections (12%), biliary leaks beyond postoperative day seven (9%), and incisional hernias (6%) (13). Abecassis et al. set out to expand this data over 12 years (14). Only 20/760 (2.6%) donor procedures were aborted, while 40% of completed donations had complications with similar percentages of bacterial infections (12.5%), biliary leaks (9.7%), and incisional hernias (6%). Following donation, the risk of residual disability, liver failure, or death (0.2-0.4%) was ~1% (14). Donation to acute liver failure patients may be considered safe to perform, as recipient survival rates (70%) and donor/recipient complication rates were reported as acceptable in the small number of acute liver failure transplants (15).

Psychological and Socioeconomic Complications

Psychological difficulties accounted for 4.1% of complications (14). Trotter et al. reported three severe psychiatric complications in the A2ALL consortium, including suicide, suicide attempt, and accidental drug overdose (16). Thankfully, Butt et al. found low rates of major depression (0-3%) and anxiety (2-3%) in the A2ALL-2 consortium at all assessments in the first two years following donation (17). Mental wellbeing was reported as impaired at various times (4.7-9.6%), but overall, donors felt like "better people" and experienced "psychological growth" (17). Looking further, Dew et al. studied outcomes three to 10 years after donation and found again that donors felt optimistic about donation (90%) (18).

However, donors also noted donation-related physical health problems and worries (15-48%) and socioeconomic concerns (7-60%) (18). The majority of donors (75%) in A2ALL-2 reported non-medical out-of-pocket expenses, 37% had donation-related medical expenses, and 44% reported these costs were a burden at two years post-donation (19). These findings suggest the need to reduce donors' financial burden, particularly those with non-professional work positions, lower-incomes, and existing financial concerns. All of the above psychological and socioeconomic studies stress a need for extensive preoperative screening and postoperative monitoring of donors, especially after recipient death. Nearly 42% of donors reported that they worried about their recipient at three months, and 25-29% were still worried at one to two years post-donation (19).

Quality of Life After Donation, Decision to Donate, and Postoperative Pain

Well-being and quality of life after liver donation are vital. Sexual dysfunction following liver donation is a known problem that affects HRQOL. At three months post-donation, abdominal pain, appearance concerns, and "not feeling back to normal" affected donor ability to orgasm, sexual desire, and general dissatisfaction with sexual life (20). However, no significant associations existed at one-year post-donation. Preoperative education and expectation management remain critical in the decision to donate. Ladner et al. assessed HRQOL over 11 years post-donation using surveys with a physical and mental component summary (21). The mean values of the physical and mental component summary were higher than those of the US population in general. However, some donors reported lower scores, which were related to education below bachelor's degree and recipient death within the last two years. Postoperative pain management varies widely across centers, with only up to five of 12 expert pain society guidelines followed in the 2016 study by Mandell et

al. (22). Emotional distress related to pain was minimal, even though >50% of donors reported adverse effects from analgesic treatment for moderate to severe pain. The need to consider pain control protocols and behavioral management, resolve concerns, and address discouragement before donation are necessary and are discussed in detail later in this review (22).

Essentials of Donor Surgical Management

Donor Right Hemi-Hepatectomy (Open Procedure)

The surgical procedure consists of five steps: 1) incision and cholecystectomy, 2) liver mobilization, 3) isolation of suitable hilar structures, 4) parenchymal dissection, and 5) division of inflow vessels, the bile duct, and the right hepatic vein. For standard cancer liver resections, the anterior approach can be adopted to reduce intrahepatic metastasis and tumor rupture for right hemi-hepatectomy for malignant liver disease. Alternatively, the Glissonian approach can be utilized for inflow vascular and biliary control in the right hemi-hepatectomy for malignant liver disease (23). However, for donor right hemi-hepatectomy, liver mobilization before parenchymal dissection is needed to reduce the ischemic time for the donor's right hemi-hepatectomy. Moreover, identification of the individual hilar structures such as the hepatic artery, portal vein, and right hepatic duct is mandatory for a donor right hemi-hepatectomy.

Traditionally, a wide abdominal incision has been preferred for the safety of the donor. However, a minimal incision, including a right subcostal or midline incision, has recently become more popular for better cosmetic results. The cystic duct is cannulated during the cholecystectomy and cholangiography is used to confirm the biliary anatomy.

After dividing the triangular ligament and detaching the right adrenal gland, the liver is entirely rotated left laterally. The retro-hepatic space is then dissected by dividing the inferior vena cava (IVC) ligament and short hepatic veins. However, the sizable accessory right inferior hepatic vein must be preserved. The right hepatic artery and portal vein are isolated in the hepatic hilum. After temporal occlusion of the hepatic artery and the portal vein, discoloration of the liver is marked, and the Cavitron® ultrasonic surgical aspirator (Integra, NJ, USA) is used to transect the parenchyma. Hepatic inflow occlusion such as Pringle's maneuver is generally avoided during parenchymal transection to avoid further ischemic injury to the donor graft. However, ischemic preconditioning may not affect the graft as well as remnant liver function (24,25). In principle, the middle hepatic vein is preserved for donor safety and sizable tributaries are temporarily clipped for backbench surgery reconstruction. When transection approaches the hilar plate, the biliary duct is divided under the guidance of real-time fluoroscopy or cholangiography with radiopaque bands. A dose of 40-50 units/kg of heparin sodium is administered intravenously three minutes before the clamping the vessels. After heparin administration, the hepatic artery, portal vein, and hepatic vein are sequentially clamped and divided. Unlike hepatectomy for diseased conditions, the vascular and biliary structures must be preserved intact. The biliary duct must be divided at the most appropriate point to avoid unnecessary multiple biliary duct openings and donor complications. Once the graft segment is removed, the systemic heparin is reversed with intravenous administration of protamine sulfate 1 mg per 100 units of heparin sodium. After closure of the abdominal wound, transversus abdominis plane block or wound filtration with a local anesthetic can be applied.

Backbench preparation of the donor graft includes venous outflow reconstruction to avoid venous congestion of segments V5, V8, and the inferior right hepatic vein and right hepatic vein. This reconstruction of significant drainage veins with 5 to 10 mm diameter is

achieved using an autologous vein or artificial vessels (26,27). According to the previous study, the liver function of the congested area with the sacrifice of prominent hepatic veins was approximately 40% in the non-congested area (28).

To be a qualified donor surgeon, sufficient experience in the surgical management of general hepatobiliary diseases such as hepatocellular carcinoma or hilar cholangiocarcinoma is mandatory. Perfectionism and precision must always be pursued in donor surgery.

Essentials of Donor Anesthetic Management

General Anesthetic Management

The anesthetic management of LDLT donors is unique in that this patient population voluntarily undertakes considerable risk for the benefit of recipients; because of this, more focus is concentrated on risk reduction and pain control.

Preoperatively, patients usually receive oral pain medications as part of a multimodal analgesic approach. Some centers also utilize neuraxial techniques to assist with postoperative pain control. Epidural analgesia, considered safe in patients undergoing donor hepatectomy with only transient deviations in coagulation status seen postoperatively, seems to provide better postoperative pain control than intravenous patient-controlled analgesics (IV PCA) (29,30). Institutions should design and implement perioperative pain management protocols that are acceptable at their own centers.

Intraoperative management prioritizes risk reduction and continues with multimodal pain management. These patients undergoing open hemi-hepatectomy need standard induction of general anesthesia and invasive monitoring placement, typically consisting of single arterial line placement and central venous access. Intraoperative fluid management has

historically involved low central venous pressure (CVP) techniques to reduce blood loss for patients undergoing liver surgery. Low CVP can be achieved with conventional fluid restriction, vasodilators, and/or diuretics. The addition of milrinone has been shown to reduce CVP and can result in an improved surgical field (31). However, CVP value as a useful indicator in decreasing hepatic congestion and lowering blood loss during hepatectomy is questionable. In general, assessment of systemic vascular volume status with CVP is challenging, as the value is affected by many factors, including the donor's cardiac comorbidities (ex., tricuspid regurgitation or diastolic dysfunction), improper alignment with the hemostatic axis, patient positioning, pressor use, or mechanical compression on the surgical field (32-34). It has been demonstrated that CVP does not correlate with intraoperative blood loss in healthy donors (35). Some authors from centers with extensive experience have even suggested that CVP monitoring may not be necessary. Its use did not result in differences in intraoperative fluid administration, hemodynamic stability, blood loss, postoperative renal function, length of hospital stay, or complications (33). Alternatively, arterial waveform-based indices, stroke volume variation (SVV), and pulse pressure variation (PPV) have been useful for volume status monitoring in both open and laparoscopic hepatectomy to decrease blood loss and achieve low venous pressure in the hepatic bed (36). SVV has been studied in patients undergoing hepatectomy, and fluid management protocols based on high SVV (10-20%) correlate with reduced blood loss. Of note, the sensitivity and specificity of SVV and PPV are negatively affected by tidal volumes less than 8 mL/kg ideal body weight, and these modalities are not applicable in patients with arrhythmias. SVV did not correlate well with CVP in periods of significant vasodilation (such as during administration of milrinone) (37). Due to the less invasive volume monitoring opportunity, some institutions avoid the placement of a central venous line altogether.

Regardless of the fluid management protocol utilized, administration of Plasma-Lyte A (pH 7.4) (Baxter Healthcare Corporation, Deerfield, IL, USA) is recommended if crystalloid infusion is needed. Lactated ringer's solution should be avoided, given the potential metabolic changes induced by hepatectomy that may impact the liver's ability to metabolize lactate. Similarly, normal saline administration can result in hyperchloremic metabolic acidosis and should also be avoided (35). Blood transfusion itself involves risks, and avoidance of heterologous transfusion is another goal of care. The use of intraoperative cell salvage, acute normovolemic intraoperative hemodilution, or preoperative autologous blood donation has proven effective in reducing the likelihood of needing a transfusion from the blood bank (38,39).

Postoperatively, donors are often admitted to the intensive care unit for close observation. Prevention of deep venous thrombosis or thromboembolic complication has paramount importance, especially for rare donors with pro-coagulant genetic makeup such as Factor V Leiden mutation. A perioperative anticoagulation regimen should be implemented per institutional protocol including the application of sequential compression devices, enoxaparin sodium, or unfractionated heparin. Early mobilization protocol is crucial. The use of Enhanced Recovery After Surgery protocols is beneficial to facilitate the recovery of LDLT donors.

Pain Management & Enhanced Recovery After Surgery (ERAS)

Significant goals of donor anesthesia management are to decrease postoperative pain, reduce nausea, decrease time to recovery of bowel function, and reduce the length of hospital stay. Pain management is of paramount importance. The A2ALL study group interviewed 245 patients before and after donation and found that up to 13% had moderate to severe pain

at some point in their postoperative course, and up to 28.8% reported poor HRQOL (40). In a single-center study, mild chronic pain persisted in 27% of patients 12 months post-donation, while pain scores dropped to levels of the general population after three years (41). The level of acute pain in the first few days of surgery is a known predictor of conversion to chronic pain. A2ALL also confirmed findings of a previous study that female donors and donors with pre-donation anxiety or certain psychosocial factors have a higher incidence of prolonged pain after surgery. Surgical factors influencing postoperative pain are right lobe hepatectomy (versus left), type of incision used for exposure, and open procedure (versus laparoscopic). Given the larger size and non-midline incision for the right hemi-hepatectomy, the donor's right hemi-hepatectomy is more painful than the donor left hemi-hepatectomy. The former requires a J-shaped, "Mercedes", or subcostal incision with xiphoid extension, while the latter can be performed with an extended midline incision. Laparoscopic donor hemi-hepatectomy decreases postoperative pain in other abdominal surgeries; however, this technique has not yet been employed widely. Developing combined surgery/anesthesia protocols using laparoscopy, multimodal analgesia, and regional or neuraxial blockade is an area of potential improvement in the pain management of LDLT donors.

Regional Anesthetic Techniques and Multimodal Pain Management

The known benefits of thoracic epidural anesthesia (TEA) in major abdominal surgery are decreased pain, improved respiratory function, and shortened return of bowel function by decreasing opioid use. Still, its use remains controversial in major hepatic resection because of the concern for post-liver resection coagulopathy and resulting epidural hematoma formation. However, two large studies on partial hepatectomy patients showed no increased risk of epidural hematoma with this technique (42,43). Koul et al. reviewed 104 LDLT

donors with subcostal incision for right hemi-hepatectomy (44) and found that TEA was not only safe, but superior to transverse abdominus plane (TAP) blocks and IV PCA. In addition, they noted that early intraoperative use of TEA resulted in a decrease of CVP due to its vasodilator effect (44). Thus, it effectively achieved a restrictive fluid state, which led to less blood loss and fewer transfusions (44,45). PubMed, Cochrane, and Google searches for publications on epidural hematoma and liver resection or hepatectomy only revealed one case report in a patient with a platelet count of 64,000/μL and a prolonged prothrombin time whose TEA catheter was removed on postoperative day (POD) 0 (46). The coagulation derangements associated with donor hemi-hepatectomy are typically resolved by POD 3 to 4, and TEA catheters can be safely removed on POD 4 or 5. As an alternative neuraxial technique, a single-shot spinal analgesic technique at pre-general anesthesia induction using morphine, morphine with bupivacaine, or bupivacaine and fentanyl can be used. This technique is associated with significant decreases in postoperative pain in the first 24-48 hours and has opioid-sparing effects (47-49). The use of ultrasound-guided TAP block with or without subcostal block (also known as a four-point block) provides pain relief in the first 12-24 hours. Although this technique did not reduce morphine equivalents past POD 0, the TAP block can be a valuable part of a recovery pathway with shortened time for diet and bowel recovery (50).

A non-opioid analgesic is an essential tool for LDLT donors. Perioperative ketamine, lidocaine, gabapentin, and magnesium have been reported as useful adjuncts with opioid-sparing effects in LDLT donors (47,51,52). Non-steroidal anti-inflammatory drugs and acetaminophen have theoretical concerns for postoperative liver dysfunction and coagulation derangements but can be used judiciously.

ERAS

As its primary goal, the ERAS Society comprehensively reviews evidence for all aspects of perioperative care in the hope of decreasing morbidity and mortality and improving a variety of outcome measures. In 2016, they published their recommendations for liver resection for liver disease and the evidence levels for each element along with grades for strengths or weaknesses. ERAS for liver resection, with both a strong evidence level and strong grade pertinent to anesthesiologists, includes: 1) allowing solid food intake up to six hours and clear liquids up to two hours before surgery, 2) avoidance of preoperative long-lasting anxiolytics, 3) prophylactic antibiotics one hour before incision, 4) avoidance of nasogastric tube use, 5) maintenance of normothermia, 6) analgesia with wound infusion catheters or intrathecal opioids combined with multimodal analgesia instead of TEA, 7) postoperative nausea and vomiting prevention with at least two anti-emetic drugs, and 8) maintenance of low CVP with a balanced crystalloid solution (53). Only one ERAS protocol for LDLT donors has been published (52). The University of Pittsburgh ERAS protocol consists of preoperative administration of intrathecal morphine, continuous IV infusions of ketamine and lidocaine throughout surgery, and local wound injection of liposomal bupivacaine at the end of the surgery. The donors receive ongoing infusions of intravenous ketamine and lidocaine postoperatively with IV ketorolac and oral acetaminophen and indomethacin. This study showed improved pain control, less narcotic requirements, and an earlier return of bowel function in those who underwent the ERAS protocol compared to the historical non-ERAS cohorts (52).

Avoidance of Blood Transfusion

Reducing the need for allogeneic blood transfusions during LDLT donation is paramount since allogeneic blood transfusion increases the risk of infection, biliary complications, and immune system modulation. The incidence of blood transfusion for LDLT donors is 9-31% (14). Mean blood loss from an experienced high-volume center for donor right hemi-hepatectomy was 261.5 ± 209.8 mL during the operation without the need for an allogeneic transfusion (54). A sizeable, single-center, retrospective study of 2,344 LDLT donor hemi-hepatectomies investigated risk factors for packed red blood cell (PRBC) and fresh frozen plasma (FFP) transfusions. In this study, 2% received PRBCs and 4% received FFP, significantly lower than the globally reported incidence of donor transfusion requirements. A multivariate regression analysis indicated that preoperative hemoglobin and a larger graft-to-donor weight ratio can predict the likelihood of PRBC and FFP transfusions, respectively (55). Careful preoperative evaluation, including preoperative optimization of hemoglobin and improved surgical and intraoperative anesthesia management, could enable safe donor surgery and avoid the need for blood transfusion (56).

Bloodless donor surgery can be achieved with stringent intraoperative fluid restriction and a high SVV until completion of resection, with no adverse effects on renal function (33,57,58). Autologous transfusion options, including intraoperative cell salvage and acute isovolumic hemodilution, have been used safely (59). Autologous blood donation did not have any proven clinical or cost-benefit (60). Inflow occlusion by the surgical team has been used to minimize intraoperative blood loss without negatively impacting donor or recipient outcomes (61).

Although coagulopathy is uncommon in LDLT donors, there is a potential for transient hepatic insufficiency following hemi-hepatectomy. Viscoelastic testing plays a role in the management of coagulopathy from massive transfusion and may be used to help with

critical decision-making in the perioperative period to help guide blood product management (62).

Miscellaneous Anesthetic Studies to Improve Donor Outcome

Recovery of the hepatic, renal, and coagulation functions of LDLT donors is critical. Several studies have compared the effectiveness of anesthetic agents in the functional recovery of LDLT hemi-hepatectomy donors. Propofol used as anesthetic maintenance has been shown to have superiority over isoflurane; propofol was reported to limit the postoperative prolongation of prothrombin time and activated partial thromboplastin time, the decrease in albumin level, and the decline of the estimated glomerular filtration rate (63). These findings are supported by a study investigating propofol's antioxidant properties in donor hemi-hepatectomy compared with isoflurane (64). Sugammadex, a newer reversal agent of neuromuscular blockade, can be safely used without worsening the bleeding tendency (65). In this study, the use of sugammadex (4 mg/kg) was also suggested to reduce anesthesia time and hospital stay.

In a study of 2,316 consecutive donor hemi-hepatectomies, intraoperative administration of albumin was associated with higher postoperative albumin levels and lower incidence of pleural effusion than synthetic colloid use (66). In another retrospective study, postoperative serum phosphate profiles were shown to significantly differ between donors with and without liver insufficiency after hemi-hepatectomy (67). Therefore, postoperative serum albumin and phosphate levels may be worth monitoring to help predict postoperative complications in donors.

Because ischemic reperfusion injury inevitably affects postoperative hepatic dysfunction, studies looking at remote ischemic preconditioning during donor hemi-

hepatectomy have significance. However, a randomized clinical trial showed that remote ischemic preconditioning by pressure inflation on the upper arm might benefit a recipient who receives a preconditioned graft, but not the donor (68).

Living donor hepatectomy has been reported being associated with significant postoperative hypophosphatemia up to 98% in equal or more than mild degree (less than 2.5 mg/dL) (69). This is considered due to increased renal fractional excretion of phosphate (70). A recent study showed that postoperative phosphate levels with the intraoperative surgical time best predicted post donation liver insufficiency (sensitivity, 90%; specificity, 55.6%) (71). Phosphorus replacement may improve recovery of hepatic function among living liver donors (69).

There are little data to suggest improvement of perioperative outcomes of any specific medication or intervention. Still, further studies are encouraged to evaluate liver regeneration and lifelong outcome after donor hemi-hepatectomy.

"Extended" Live Donor Consideration

LDLT donors are essentially healthy patients with minimal comorbidities under good medical control (72,73). However, for an LDLT in an emergent situation, such as in a Status 1 recipient, the donor evaluation processes may require expedition and donor eligibility may be expanded (74). The use of non-standard "extended" live donor candidates imposes significant anesthetic and ethical challenges; therefore, anesthesiologists must participate in the decision-making process. In a reported case, an 18-week pregnant patient successfully underwent a left hemi-hepatectomy as a donor for her one-year-old daughter who had rapidly worsening liver failure from biliary atresia (75). Pregnancy is typically considered an absolute contraindication to donation, but this was an extraordinary case where many ethical

and clinical questions were posed. In another case report, a donor had their evaluation fast-tracked and completed within 24 hours without compromising ethical or safety concerns (74). The expedition of donor suitability evaluation should only be considered in emergency cases if a multidisciplinary team is available to support such a need (75). Although exceptional cases are usually reported as successful, the risks related to donor hemi-hepatectomy are significant, and any mortality has devastating effects on patients and families. Additionally, such a grave incident can put a transplant program itself at risk. Therefore, high-risk donation should only be considered after all other options have been exhausted.

Innovative Surgical Techniques and Anesthesia Management

Laparoscopic Donor Surgery and Anesthesia

Laparoscopic liver surgery has become more popular as a surgical technique because it offers many benefits including fewer overall complications, less blood loss, lower pain, a better quality of life, and a shorter hospital stay compared with open liver surgery (76-80). Recently, the laparoscopic technique has been introduced for the LDLT donor hemi-hepatectomy procedure. With the advancement of surgical techniques and laparoscopic equipment, many transplant centers began to adopt this new modality as the standard for LDLT donor hemi-hepatectomies (81-87). In the early stage of development, laparoscopic procedures were reserved for small graft resections (81,85). However, more extensive graft resections such as right hemi-hepatectomies have become feasible when experienced surgeons perform the surgery, with outcomes like those for open donor surgery (76,86,87). Initially, laparoscopic donor right hemi-hepatectomy was performed using a hand-assisted approach through a subxiphoid vertical incision (88). Still, more recently, pure laparoscopic

donor right hemi-hepatectomy (PLRH), which is more technically complex with a steep learning curve, has been attempted in a few highly specialized centers. PLRH has been demonstrated to produce similar surgical outcomes comparable to those of the open approach but with less adverse event profiles, including decreased pulmonary complications, less postoperative pain, and faster hospital discharge (76,82,84,86,87,89). A recently published systematic review and meta-analysis compared the short-term safety and efficacy of minimally invasive donor right hepatectomy (MI Group) with open donor right hepatectomy (Open Group) using the 12 studies with a total of 1,755 donors (90). Compared to Open Group, MI Group had less bleeding (standardized mean difference [SMD] -0.52, $p<0.001$), shorter hospital stays (SMD -0.58, $p<0.001$), and lower overall postoperative donor complications (RR 0.74, $p=0.008$). There were no statistically significant differences between MI Group and Open Group in postoperative liver function, rate of major complications and vascular complications of both donors and recipients, and overall postoperative complications. MI group was associated with prolonged operative times (SMD 0.74, $p<0.001$), as well as a higher rate of biliary complications in donors (relative risk [RR] 2.26, $p=0.007$) and recipients (RR 1.69, $p<0.001$) (90).

Surgical Procedure (87)

First, an intraoperative biopsy is performed to determine the suitability of the organ donor. The donor is positioned in the supine position, and a three-dimensional laparoscope is used. For PLDH, five trocar ports are placed as follows: one 12-mm port receiving a 30° optic device at the umbilicus; one 12-mm operative trocar each at the right midaxillary line and the midline; and two 5-mm trocars for instrumental assistance, one at the left midclavicular area and one in the subxiphoid region. Intra-abdominal pressure is maintained

at around 10 mmHg with carbon dioxide gas. The liver is mobilized to identify the right hepatic vein at the cephalad direction and the IVC at the caudal direction. The cystic duct is resected, and the remnant duct at the biliary side is preserved for traction while dissecting the right hepatic artery and vein. After dissection of the vessels, a temporary vessel clamp is applied to identify a demarcation line.

During the initial parenchymal separation, proper traction is maintained by pulling the fundus of the gall bladder to the right side and the teres ligament to the left side. The direction is from the caudal side to the cephalad side during parenchymal separation because it is fast and safe. For transection, Harmonic Ace® (Ethicon Endosurgery, Medtronic, Minneapolis, MN, USA) or Sonicision™ (Covidien, Medtronic, Minneapolis, MN, USA) is first used until the middle hepatic vein level. After passing the middle hepatic vein level, the Cavitron® ultrasonic surgical aspirator (Integra, NJ, USA) is used to reduce unnecessary damage to the adjacent tissues. The portal vein and artery are taped with vessel loops and tracked to the abdominal wall while dissecting the caudate lobe. This isolated bile duct is incised and then encircled with a silk thread. Afterward, it is dissected under the guidance of an intraoperative cholangiogram or ultrasonogram. Intraoperative ultrasound is used after temporarily clamping the common bile duct to induce congestion to dilate the bile duct for easier detection and identification. After completing the parenchymal traction, the small hepatic veins to the right side of the liver are clipped, while more prominent veins are preserved. The liver graft is then wrapped in an endo-bag, and a Pfannenstiel incision is made. The hepatic artery, portal vein, and inferior hepatic vein are ligated with a Hem-o-lock clip. After ligating the right hepatic vein, the graft is extracted and removed through the Pfannenstiel incision. Finally, the remaining left falciform ligament is anchored and a drain is inserted.

Anesthesia Management

Standard anesthesia monitoring for laparoscopic donor hemi-hepatectomy includes electrocardiography, pulse oximetry, invasive radial artery blood pressure, esophageal temperature, neuromuscular block monitor, and bispectral index. A central venous catheter may not be mandatory for large transplant centers with experienced transplant teams. Attending anesthesiologists can choose the types of anesthesia induction and neuromuscular blocking agents they prefer, and anesthesia is maintained either with volatile or IV agents. Mechanical ventilation is administered with a tidal volume of 6-8 mL/kg and a positive end-expiratory pressure of 6 cmH_2O using a mixture of medical air and oxygen (fraction of inspired oxygen at 0.5). The ventilation frequency can be adjusted to maintain the E_TCO_2 at 4.0-5.7 kPa. Volume or pressure-controlled modes can be used depending on the preference of the anesthesiologist. During laparoscopic surgery, the intraperitoneal pressure is adjusted to 10 ± 2 mmHg after inflation of the abdominal space, and the 30° reverse Trendelenburg position is established. After graft removal and stabilization of hemostasis, the CO_2 gas supply is stopped, and the patient is returned to the level-supine position. For postoperative pain control, several strategies have been used and reported, including TEA, intrathecal morphine, or IV PCA (91), continuous wound infusion of ropivacaine (92), and various fascial blocks including bilateral single-injection erector spinae plane (ESP) block (93), bilateral continuous ESP block with catheter technique (94), and most recently, bilateral quadratus lumborum type 2 block. In conclusion, a multimodal approach including regional anesthesia should be considered as the basis of any analgesic plan for LDLT donors.

Robotic Donor Surgery and Anesthesia

Since the first report in 2012, a slow but steady increase in robotic donor hepatectomies has been reported. Utilizing robotic surgery can overcome several technical limitations encountered with standard laparoscopic hemi-hepatectomies, such as the loss of visual depth perception due to two-dimensional visualization and constrained maneuverability of the instruments. Recent studies comparing robotic laparoscopic versus open donor hemi-hepatectomies have shown several advantages with the robotic technique (95), including decreased in-hospital stay, reduced blood loss, and an overall reduction in complication rates (96,97). Moreover, compared to the open procedure, the introduction of robotic laparoscopic donor hemi-hepatectomies has been shown to minimize the size of skin incisions, resulting in decreased scarring and related abdominal wall complications, earlier postoperative ambulation, and earlier return to normal activities (98). However, operative time was shown to be increased with the robotic procedure (95). Currently, only a few transplant centers in the United States have performed robotic laparoscopic donor hemi-hepatectomy, likely due to significant initial investment and maintenance costs and the need for a highly specialized surgical team.

Robotic donor hepatectomy may presents anesthetic challenges, including patient positioning (15–20-degree reverse Trendelenburg position), limited patient access, close volume status monitoring with CVP or SVV during hepatic dissection, increased procedural duration, hemodynamic and respiratory effects of the pneumoperitoneum, occult blood loss, and the potential for conversion to an open procedure. However, the new generation robot platform such as the da Vinci® Xi™ system (Intuitive Surgical Inc., Sunnyvale, CA, USA) has made these conditions less challenging with its smaller size, lesser requirement of reverse Trendelenburg positioning, and the lesser degree of pneumoperitoneum requirement at 12-13 mmHg. Massive bleeding is a potential concern during any form of hepatic surgery, especially with a standard laparoscopic surgery. However, the ability to perform bleeding

control is much more effective with the robotic platform than the laparoscopic one with EndoWrist instruments (Intuitive Surgical Inc., Sunnyvale, CA, USA), including blunt and sharp endoscopic dissectors, scissors, scalpels, forceps / pickups, needle holders, endoscopic retractors, and electrocautery and accessories.

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Table 1: Living donor graft choice

	Advantages	**Disadvantages**	**Requirements**
Right Lobe	good volume for recipient	large loss of donor volume (≈70% SLV)	donor to maintain ≥ 30% SLV after donation
Left/Caudate Lobe	better volume than left lobe alone helps to overcome		

	SFSS		recipient to receive ≈ 0.8
Left Lobe	good volume for small recipients less donor liver removed	small, donated mass/volume risk of SFSS	
Dual Grafts	helps to overcome donor/recipient size mismatch	needs to be performed in highly specialized centers	

Abbreviations: SLV, standard liver volume; SFSS, small for size syndrome; GRWR, graft-to-recipient weight ratio