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**Split liver transplantation: What’s unique?**

Dalal AR. Split liver transplantation

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**Abstract**

The intraoperative management of split liver transplantation has some unique features as compared to routine whole liver transplantations. Only the liver has this special ability to regenerate that confers benefits in survival and quality of life for two instead of one by splitting livers. Primary graft dysfunction may result from small for size syndrome. Graft weight to recipient body weight ratio is significant for both trisegmental and hemiliver grafts. Intraoperative surgical techniques aim to reduce portal hyperperfusion and decrease venous portal pressure. Ischemic preconditioning can be instituted to protect against ischemic reperfusion injury which impacts graft regeneration. Advancement of the technique of split liver transplantation is essential as use of split cadaveric grafts expands the donor pool and potentially has an excellent future.

**Key words:** Split liver transplantation; Small for size syndrome; Graft to recipient body weight ratio; Hemiliver grafts; Portal hyperperfusion

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**Core tip:** The liver has a special ability to regenerate that confers benefits in survival and quality of life for two instead of one by splitting livers. Primary graft dysfunction may result from small for size syndrome. Graft weight to recipient body weight ratio is significant for both trisegmental and hemiliver grafts. Intraoperative surgical techniques aim to reduce portal hyperperfusion and decrease venous portal pressure. Ischemic preconditioning can be instituted to protect against ischemic reperfusion injury which impacts graft regeneration.

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**INTRODUCTION**

Liver parenchyma is able to regenerate. Additionally, the liver vasculature has lobar and segmental distributions. Thus, the liver is considered to be a double organ and offers benefits in survival and quality of life for two instead of one recipient, by means of dividing or splitting a graft.

**SMALL- FOR –SIZE-SYNDROME**

Primary graft dysfunction can result from the use of partial livers despite the absence of other causes such as vascular obstruction or sepsis. This increasingly recognized phenomenon is termed as “Small-For- Size -Syndrome (SFSS)”[1].

The graft exhibits signs of primary graft dysfunction within the first postoperative week. This dysfunction is in absence of other diagnosis such as vascular obstruction, biliary leak, sepsis and immune rejection. Coagulopathy, bilirubinemia and ascitis are typical manifestations of SFSS[2]. SFSS has been studied extensively in both, humans as well as animals.

It has been suggested that portal hyperperfusion of the graft combined with poor venous outflow and reduced arterial flow might cause sinusoidal congestion and endothelial dysfunction, resulting in SFSS. Graft related factors such as graft to recipient body weight ratio < 0.8, impaired venous outflow, steatosis > 30% and prolonged warm/cold ischemia time are positively predictive of SFSS[1].

Another study states that the lower limit of the graft weight to recipient weight ratio can be safely reduced to 0.6% in adult-to-adult living donor liver transplant, if portal pressure control is used[3].

**GRAFT ALLOCATION**

Though a split liver maybe obtained from a standard criteria donor, splitting it creates two extended criteria grafts, thus increasing the risk of graft failure[4,5]. There are also ethical dilemmas associated with ownership and stewardship of the organs. Is it ethical for a patient to request for an entire organ rather than a split component[6]? There is increased risk of biliary complications with a split liver, and a recipient may wish to thus decline it. Would it be considered coercion if the patient on the top of the waiting were told that if they declined to a splitting of the liver it would be given to the next on the list[6]?

Other considerations include use of the unassigned part of the graft. As per the United Network for Organ Sharing allocation policy, the unassigned part has to be allocated according tot the waiting list and cannot be used by the center performing split liver transplantation (SLT). If an incentive is created by allowing the unassigned part of the liver to be retained by the organization, then the number of split livers in the United States will increase[7].

**INTRAOPERATIVE FEATURES**

The liver can be split *in situ*, on the back table or in the donor hospital before the donor cross-clamp. Notable advantages are a decrease the total ischemia time and increase in the possibility of inter-center sharing. It may take an additional 1-2 h to perform cholangiogram, hilar dissection and parenchymal division. Cholangiogram can be performed to assess surgical splitability[8].

Contrast enhanced computed tomography could be used to perform a virtual resection and volume analysis. Prior to an *in situ* split, one can determine the segmental volume and delineate surgical planes. The anatomy of the hepatic vasculature and biliary structures can be determined. The anticipated graft and remnant liver volumes post resection can be calculated. The severity of portal hypertension can be assessed using a triphasic computer tomographic scan[9]. Liver grafts are then perfused and preserved with Histidine-Tryptophan-Ketoglutarate solution (Custodiol Solution; Essential Pharmaceuticals, Newtown, PA)[8].

Excellent results have been reported with split livers. These are a right tri-segmental graft that includes segments I, IV, V, VI, VII, and VIII; and a left graft consisting of the left lateral lobe including segments II and III. Pediatric recipients are usually transplanted with the left lateral lobe. The right tri-segmental graft is usually transplanted into an adult recipient[1].

The liver’s regeneration capacity is compromised by aging. Therefore acceptable donor age is usually less than 50 years[10]. However, the major challenge in the field of liver transplantation is organ shortage[11-14].

The split liver technique has been further expanded to use two hemiliver grafts: a left lobe and a right lobe, which effectively expands the donor pool. Unfortunately, however, many challenges have surfaced[7,15-17]. Some challenges and unfavorable outcomes have made many transplant centers reluctant to use hemiliver grafts[16,17]. Since the Model for End-Stage Liver Disease (MELD) allocation uses the sickest first policy, livers amenable to splitting are most often allocated to patients unsuitable for SLT.

The middle hepatic vein (MHV) is considered “dominant” in drainage of the hemiliver in 27% of cases[18]. A right hepatectomy without the MHV or reconstruction can induce congestion of the paramedian segments V and VIII, reducing functional capacity of the graft. When graft survival was analyzed, no significant difference was found with or without harvest of the MHV, as long as a vein interpositional graft was used for anastomosis[19,20]. The MHV primarily drains the right anterior lobe and segment IV. On the other hand, a meta-analysis discovered that there was better functional recovery of patients who received the right lobes with MHV[21].

It maybe beneficial to maintain a low central venous pressure (CVP) to minimize graft hyperperfusion. Additionally, low CVP decreases backflow bleeding from the hepatic veins and decrease bleeding during parenchymal transection[22]. An analysis stated that patients with a CVP < 5 cm H2O had a median blood loss of 200 mL, whereas those with CVP > 5 cm H2O had a median blood loss of 1000 mL[23]. Low CVP facilitates safe dissection of the retro-hepatic vena cava and major hepatic veins and produces decreased postoperative morbidity and reduction of hospital stay[24]. The potential disadvantages of low CVP anesthesia are chances of perioperative embolism, need for pressor agents and postoperative renal dysfunction.

The partial clamp inserted in the piggyback method allows some venous return, thereby preventing an acute reduction in the preload during inferior vena cava cross clamping. When the patient is unable to tolerate the test cross clamp, it may be prudent to consider venovenous bypass. Presently, in the United States, temporary portocaval shunt is routine practice in 29% of programs, and a low CVP technique is practiced in 54% of centers[25].

The liver weight can be estimated as 2% of donor’s body weight, divided into approximate weights of 35% for the left lobe and 65% for the right lobe[8]. It is important to note that since small-for-size grafts require vigorous and immediate hepatocyte proliferation, regeneration is critically required for the success of SLT. In rats, remnant liver of 10% maybe enough. However, in humans, more volume is required for transplantation[26]. Though at three months after partial liver transplantation (50%, 60% size) liver volume slightly exceeds 100% of the standard liver volume in recipients. The graft increase ratio is higher in 50 % partial LT as compared to 30% partial LT[27].

The liver receives approximately 25% of the cardiac output, of which 75% is supplied by the portal vein and the other 25% by the hepatic artery. Hepatic blood flow is reduced by all anesthetic agents and techniques via reductions in hepatic blood flow and hepatic oxygen uptake[28].

Intraoperative factors that decrease hepatic blood flow are mechanical ventilation, hypercarbia, positive end expiratory pressure, hypotension, hemorrhage, hypoxemia and surgery. If the decrease in hepatic blood flow is significant, it can result in parenchymal centrilobular necrosis[28]. Etomidate, ketamine and propofol are induction agents. Etomidate decreases hepatic blood flow[29]. Ketamine has little impact on hepatic blood flow. Propofol has a vasodilator effect, ultimately increasing total hepatic blood flow[30,31]. Midazolam has a longer half-life, a reduced clearance, reduced protein binding, a longer duration of action and an enhanced sedative effect. Dexmedetomidine, an alpha-2 adrenergic agonist, with sedative and analgesic properties, is primarily metabolized in the liver[32]. All volatile anesthetics decrease the mean arterial pressure and portal blood flow. Desflurane and sevoflurane have very little or no effect on total hepatic blood flow[33].

The elimination half-life of morphine is prolonged in cirrhosis. The sedative and respiratory depressant effects are exaggerated. Fentanyl has a short duration of action and its elimination is not appreciably altered in patients with cirrhosis[34]. However, unlike fentanyl, plasma clearance and elimination of alfentanil is increased in patients with cirrhosis[35]. Remifentanil is a short acting synthetic opioid that is hydrolyzed by blood and tissue esterases. Its pharmacokinetics is unaltered in patients with severe liver disease[36].

Vecuronium and rocuronium are steroidal muscle relaxants that are metabolized by the liver. In cirrhotic patients, they have decreased clearance, prolonged half-lives, and prolonged neuromuscular blockade. In living donor liver transplantation, requirements of vecuronium were least in the neohepatic phase[37]. Suggammadex can reverse rocuronium rapidly[38]. Cisatracurium undergoes ester hydrolysis and cisatracurium infusions during liver transplantation require increased dosages and result in prolonged recovery[39].

Ischemic preconditioning protects against ischemic reperfusion injury (IRI) in liver transplantation. Lower aspartate aminotransferase levels and significant reduction of moderate-severe hepatocyte swelling is seen[40]. In rat liver, morphine preconditioning protects against IRI. This involves opioid receptors, phosphatidylinositol-3-kinase, and Akt[41]. IP protected against hepatic IRI under isoflurane anesthesia in rats. The mechanism of protection appeared to involve upregulation of Bcl-2 expression resulting in inhibited apoptosis[42]. Human studies have revealed that patients preconditioned with sevoflurane experienced a reduction in peak transaminase levels, an improvement in clinical outcomes, and enhanced benefit in those with steatotic livers. Inducible nitric oxide synthase mRNA was significantly increased in the preconditioned group suggesting a role for nitric oxide[43].

Unfortunately, ischemic preconditioning significantly enhances the extent of split liver graft injury and hinders hepatic regeneration in SFS liver transplant models[44]. Interestingly, rather than IRI, a shift in regeneration ability is more likely to cause liver graft dysfunction and failure following small-for-size transplantation.

Portal hyperperfusion has been cited as one of the causes for SFSS. Thus the most important step is prevention of small-for-size syndrome through perioperative treatment strategies include reduction of portal blood flow[45]. Lowering the graft perfusion pressure is vital. Hepatic venous congestion due to insufficient vascular orifices or mechanical stenosis and kinking should be prevented[45].

Surgical approaches to prevent SFSS fall into two categories. The first targets portal hyperperfusion by reducing inflow to the graft, including splenic artery modulation and portacaval shunts. The second aims to relieve parenchymal congestion[1]. Adenosine washout maintains the hepatic arterial buffer response (HABR) that maintains constant total blood flow to the liver. Portal blood flow removes adenosine that has a local vasodilator effect on the arterial system[46,47]. However, an exaggerated HABR may contribute to ischemic injury in states of portal hyperfusion, as seen in small for size grafts[48,49]. Prophylactic splenic artery modulation[50,51] produced a significant reduction in portal flow causing a significant reduction in incidence of SFSS.

SFSS grafts are also at least partly associated with persistent elevation of portal venous pressure[52]. Vasopressin infusions have been used in certain institutions to decrease portal pressures and flow prior to the anhepatic phase[53].

**CONCLUSION**

The following factors such as changes in recipient and donor selection and matching, changes in allocation and logistics, and improved technical proficiency have influenced outcomes. The risk of graft failure is now similar between split and whole-liver recipients[54].

There are several challenges, and routine application of the hemiliver technique is still controversial, but can achieve excellent outcomes under the model for end-stage liver disease allocation[8]. The 5-year graft survival for hemilivers is comparable to whole livers[8]. Split liver transplantation, which is based on this unique ability of the liver to regenerate, is an excellent idea to increase the donor grafts. Through the expansion of split-liver transplantation, the transplant community might be able to both increase the organ pool and bridge the liver demand-supply gap.

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