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Inflow Modulation in Adult Living Donor Liver Transplant to Reduce Risk of Small-for-Size Syndrome (SFSS)

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Abstract

Small for Size Syndrome (SFSS) is a specific problem in Living Donor Liver Transplant (LDLT) where the pathogenesis in SFSS seems to be primarily linked to graft over perfusion. Various methods of modulating portal inflow to reduce excessive flow to the liver without compromising liver function has been described. We report the outcome of 4 LDLT cases in which the portal inflow was modulated by performing a splenectomy and a temporary hemi-portocaval shunt.

Keywords: Liver transplant; SFSS; LDLT; DDLT

Introduction

Living Donor Liver Transplantation (LDLT) is an increasingly common modality of liver transplantation in the East due to shortage of cadaveric grafts [1]. Improvements to the selection and safety of LDLT has been improved over the past decades, making the contemporary results of LDLT comparable to deceased donor liver transplantation (DDLT) However, specific problems arising from living donor liver transplant (LDLT), such as size mismatch between donor and recipient are still significant challenges to overcome [2].

Small for Size Syndrome (SFSS) was recognised in the early days of LDLT where liver failure was observed in patients who received small grafts relative to their body weight. A Small for Size Graft (SFSG) was later defined as a liver graft with a Graft Weight Ratio (GWR) of <0.8 [3]. This was a significant issue overcome as SFSS was reported to be as high as 40% in LDLT [4]. Sugawara et al. [5] described the problems of SFSG in a series of 80 LDLT observing that hyperbilirubinemia and prolonged Prothrombin Time (PT) persisted longer in the group with SFSG [5]. Subsequently, SFSS was defined as graft dysfunction in the first postoperative week characterized by the presence of hyperbilirubinemia, coagulopathy or ascites on 3 consecutive days [6]. Even though not fully understood, pathogenesis of SFSS seems to be primarily linked to graft over perfusion [2]. Various methods of modulating portal inflow to reduce excessive flow to the liver without compromising liver function have been described. However, there is no consensus as to which method is superior [3]. In our centre, our technique of choice to modulate the inflow of the grafts in ALDLT with GWR <0.8 comprises of a splenectomy and a temporary hemi-portocaval shunt. Here, we report the outcome of 4 ALDLT cases with inflow modulation as described above.

Patients and Methods

Recipients

From 2015 to 2017, we performed a total of 4 LDLT using liver grafts with a GWR <0.8 in a single centre. All 4 recipients are male. Two patients had Non-Alcoholic Steatohepatitis (NASH) related liver cirrhosis complicated with Hepatocellular Carcinoma (HCC), 1 patient had Hepatitis B Virus (HBV) related liver cirrhosis complicated with HCC where the last patient had Hepatitis C Virus (HCV) related liver cirrhosis complicated with HCC. All 4 patients had clinically significant portal hypertension before transplant. After transplant, all donors were put on a standard protocol of immunosuppressive agents comprising of Mycophenolate Mofetil (MMF), Basilixumab, Tacrolimus and Prednisolone.

Grafts

Living donor right hepatectomy was performed for all 4 cases. In cases where the middle hepatic vein was not harvested, reconstruction of the venous outflow for segments 5 and 8 was performed

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Table 1: Characteristics of liver grafts.

	Left/right lobe	Actual graft weight (g)	Graft-weight ratio (GWR)
1	Right	538.5	0.66
2	Right	558.0	0.65
3	Right	691.0	0.78
4	Right	574.0	0.71

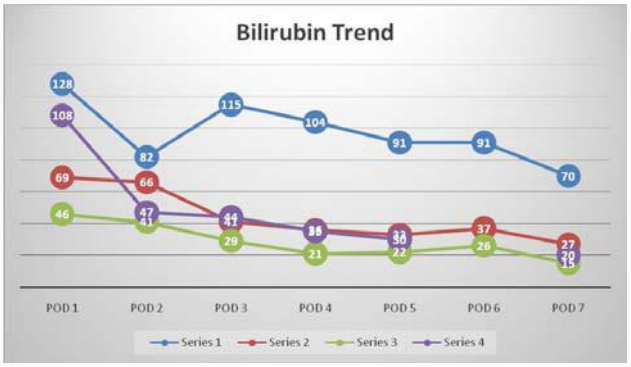

Figure 1: Bilirubin trend of recipients in first post-operative week.

with iliac vascular conduits. The actual graft weight was calculated for all recipients. Graft characteristics are summarized in Table 1.

Surgical technique

All 4 recipients had a splenectomy and a temporary hemi-portocaval shunt created between the right branches of the portal vein to the inferior vena cava. The hemi-portocaval shunt was ligated after reconstitution of the graft hepatic venous outflow and portal venous inflow. The portal pressure was measured before and after portal inflow reconstruction. Hepatic artery reconstruction was performed with end to end arterial anastomosis in all 4 recipients under microscope by the plastic and reconstructive surgeons. Biliary anastomosis was performed in an end-to-end fashion between the donor and recipient bile ducts.

SFSS and encephalopathy

In our case series, we used the definition proposed by Dahm et al. [7] for SFSS. Dahm et al. [7] proposed definition for small for size dysfunction as dysfunction of a small partial liver graft (GWR <0.8%) during the first postoperative week after the exclusion of other causes like technical, immunological or infectious causes. Graft dysfunction was defined as the presence of two of the following on three consecutive days: bilirubin >100 μmol/l, INR >2, encephalopathy grade 3 or 4.

Results

Donors and grafts

All four donors recovered uneventfully, and no repeat interventions were required. Length of Stay (LOS) for all donors ranged from 6 to 8 days.

Outcomes of 4 recipients

Intraoperatively all liver grafts appeared well perfused with no evidence of congestion after all anastomosis were completed. Portal pressure measured before and after inflow modulation and completion of anastomosis showed significant reduction. All 4 recipients were discharged with a LOS ranging between 11-67 days. 1 patient had complete thrombosis of the hepatic artery anastomosis and required

Table 2: Intraoperative modulation of portal inflow.

	Splenectomy performed	Hemi-portocaval shunt performed	PVP (before anastomosis)	PVP (after anastomosis)
1	Yes	Yes	30 mmHg	16 mmHg
2	Yes	Yes	21mmHg	15 mmHg
3	Yes	Yes	30 mmHg	15 mmHg
4	Yes	Yes	19 mmHg	16 mmHg

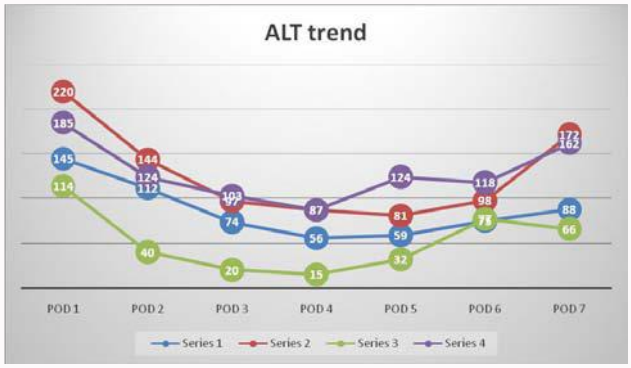

Figure 2: ALT trend of recipients in first post-operative week.

a re-operation for takedown of thrombosed arterial anastomosis with re-do arterial anastomosis with left radial artery graft. He was started on single agent anti-platelet and subsequently monitored with ultrasound Doppler of the hepatic arterial anastomosis. No further thrombosis occurred, and patient was discharged well.

Primary non-function of the liver graft did not occur in any patients. Bilirubin was trended for the first postoperative week and patients were observed clinically for development of encephalopathy to detect early graft dysfunction and development of SFSS. All four patients have down trending bilirubin as shown in Figure 1. None of the recipients had encephalopathy.

Acute biochemical rejection occurred in 3 patients, who presented with elevated liver transaminases. They were otherwise clinically asymptomatic. Liver biopsy performed in one patient showed features consistent with acute rejection with a rejection activity index 5/9, portal inflammation 2, bile duct inflammation damage 2 and venous endothelial inflammation 1. Both acute rejection episodes were treated successfully with pulsed steroids. Trend of liver transaminases is shown in Figure 2 and Figure 3. At the time of concluding our case series, all four liver grafts were functioning well at an interval follow up of 5-26 months.

Discussion

Liver transplant is the only curative treatment for patients with advanced liver failure and hepatocellular carcinoma [8]. With the progress of surgical techniques and understanding of graft anatomy, LDLT emerged as a mainstream modality of transplantation. However, its expansion slowed down due to the occurrence of SFSS. This was especially so in the Western countries where the donor morbidity and risk of SFSS potentially outweigh the benefits of performing LDLT with SFSG. Furthermore, because the deceased donor pool is larger, LDLT with its attendant risks to the donor and SFSS make it a controversial option [9].

Although SFSS can potentially be avoided by using the larger

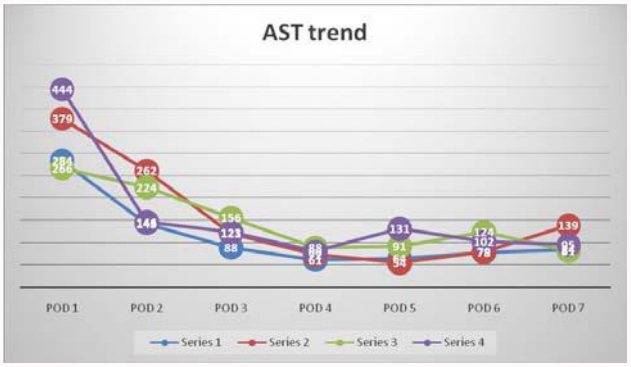

Figure 3: AST trend of recipients in first post-operative week.

right lobe graft, Umeshita et al. [10] reported a higher frequency of complications in donors of the right liver lobe compared to donors of lateral segment or left lobe [10]. Use of a smaller liver graft, though reducing donor morbidity and mortality, is limited by risk of developing SFSS and vulnerability to other insults such as sepsis during recovery period [2,11].

Though not well understood, SFSS appears primarily linked to graft hyperperfusion. Poor outcomes have been reported in LDLT with SFSG likely due to excessive portal venous inflow which causes a diffuse ischemic pattern with cellular ballooning noted on liver biopsies [12,13]. To improve SFSG survival, many have proposed to modulate portal inflow to prevent graft hyperperfusion. As portal vein flow accounts for over 90% of total liver flow, [14] it is reasonable to modulate portal inflow to prevent SFSS in recipients with GWR <0.8. Troisi et al. [2] reported a poorer outcome in SFSG without inflow modulation compared to those with inflow modulation [2].

The decision to perform inflow modulation relies on the clinical judgment of the surgeon and the severity of portal hypertension at transplantation. There is no fixed threshold of portal vein pressure in deciding to perform portal inflow modulation to reduce portal hyperperfusion. Troisi et al. [2] concluded in a study that PVF of 250 ml/min per 100 g liver is a suitable target level to prevent SFSS [2]. Kyoto group described a retrospective series and concluded that patients with a portal pressure of <15 mmHg demonstrated a better survival rate that patients with portal pressure >15 mmHg [15]. Our unit's practice is to modulate the inflow of all recipients with a GWR of <0.8 to prevent SFSS. In our series, all four patients with inflow modulation of portal flow did not develop SFSS or early graft dysfunction requiring re-transplantation.

The use of Splenectomy or Splenic Artery Ligation (SAL) as a simple and safe method to modulate portal flow has been reported [2,16,17]. If this is insufficient to relieve portal hyperperfusion, other techniques such as hemi-portocaval shunts, banding or porto-mesenteric disconnection should be considered [14]. Troisi et al. [2] reported excellent graft survival in using hemi-portocaval shunt to modulate portal inflow in recipients with GWR <0.8 [9]. However, significant concerns have been raised due to the worry that excessive portal shunting carries a risk of hepatofugal flow which could lead to graft dysfunction, portal thrombosis or impairment of graft regeneration capabilities [18]. Yamada et al. proposed utilization of a hemi-portocaval shunt based on portal vein pressure more than 20 mmHg at the time of transplant in recipients with GWR between 0.6-0.8. In this study, there were no significant negative impacts of the persistent shunt on graft regeneration capabilities.

In our centre, modulation of graft inflow of SFSG was achieved by performing a splenectomy with a temporary hemi-portocaval shunt for our recipients with a GWR <0.8. With the portal flow modulated, there was a significant drop of portal pressure before and after completion of anastomosis (Table 2), signifying successful reduction of portal flow to the small partial liver grafts. This was a durable procedure evidenced by the sustained reduction of portal pressure even after ligation of the hemi-portocaval shunt. As our patients did not develop SFSS, we concluded that this is a safe method to modulate inflow of portal vein without further compromising the graft regeneration capabilities.

In our series, we have demonstrated a safe and yet efficient way to modulate the portal inflow in order to prevent development of SFSS in SFSG. Maturation of this technique might lead to more ALDLT cases with smaller liver grafts that could potentially benefit would be recipients without compromising the safety of the donors.

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