Impact Of Reconstructing A Single Hepatic Artery On Small-For-Size Grafts In Living Donor Liver Transplantation

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Citation

Abstract
Introduction. The recent outcomes of living donor liver transplantation (LDLT) using small for size grafts (SFSG; graft recipient weight ratio; GRWR <0.8) along with portal vein flow modulation has shown encouraging results. However, these liver grafts can at times have two hepatic arterial stumps. This can result in a dilemma whether to reconstruct a single or both arteries. Hepatic artery (HA) thrombosis is the most dreaded complication in LDLT as it can result in graft loss and re-transplantation. We herein report the feasibility of reconstructing a single HA in LDLT having two arterial stumps in the liver grafts with GRWR<0.8.

Methodology. From 2005 to 2010, 50 patients undergoing LDLT with GRWR<0.8 and having multiple HAs, were retrospectively analyzed and divided into Group 1 (n=28): 2 HA stumps with 1 HA reconstruction and Group 2 (n=22): 2 HA stumps with 2 HAs reconstruction. The decision regarding the reconstruction of single or multiple HAs was made depending on the pre-operative radiological and intraoperative assessments. Recipient portal vein flow modulation was done whenever necessary. Outcomes with respect to graft dysfunction, graft loss and patient mortality were compared between the groups.

Results. The incidence of graft dysfunction was similar among the 2 groups (p=0.418). The incidence of biliary strictures and HA thrombosis was similar among the groups. There was no graft loss or patient mortality due to graft dysfunction.

Conclusion. Single HA reconstruction does not increase the risk of graft dysfunction in recipients undergoing LDLT having GRWR<0.8 and dual hepatic arterial stumps in the liver graft.

LDLT: living donor liver transplantation
HA: hepatic artery
SFSG: small-for-size graft
SFSS: small-for-size syndrome
PVFR: portal vein flow rate
MELD: model for end stage liver disease
GRWR: graft-to-recipient weight ratio
DUS: Doppler ultrasound
CTA: CT angiogram
INR: international normalized ratio

INTRODUCTION
Adult-to-adult liver transplantation has gained widespread acceptance as the standard treatment modality for end stage liver disease patients. Over the last few decades, there has been a shift in the paradigm from deceased to living donor liver transplantation (LDLT), due to the ever decreasing pool
of deceased liver donors. Although living donor livers provide a very high quality of livers as compared to those from deceased donors, there is always an ongoing concern regarding sufficient transplanted liver graft volume to avoid any deleterious effects in the recipient. Therefore, the issue of graft-size matching, to obtain the best outcome for the recipient, is a significant concern in LDLT (1-5). Indeed many liver transplantation centers have arbitrarily suggested a graft-to-recipient weight ratio (GRWR) to be at least 0.8, our anecdotal experience suggested that even small-for-size grafts (GRWR<0.8) can have favorable outcomes (6-7).

In general, small-for-size grafts (SFSG) are prone to graft dysfunction hence utmost care is taken to reconstruct all the venous outflows, more close monitoring of liver functions, alterations of immunosuppression regimens and lower threshold for diagnostic biopsies. In the wake of all this, these grafts can at times have presence of multiple hepatic arteries (HA). Early HA thrombosis is a devastating complication and can result in graft loss and re-transplantation. This raises the question if reconstruction of all the HAs is really necessary in the setting of SFSG. Also whether only single HA reconstruction can have any deleterious effect on the regeneration liver graft is not known. The impact of reconstructing only a single HA on the occurrence of graft dysfunction in liver grafts with GRWR <0.8 has never been documented previously. We herein report our results of reconstructing a single HA in presence of dual HAs in liver grafts with low GRWR (<0.8) in LDLT.

**METHODOLOGY**

We prospectively analyzed the database of all recipients undergoing LDLT at Kaohsiung Chang Gung Memorial Hospital, Taiwan, from 2005 to 2010. All potential donors with estimated GRWR <0.8 were evaluated for eligibility for the procedure as long as the remnant liver volume in the donor would be >30%. The recipients were well informed about the risk of graft failure due to small graft size. None of the transplants were aborted due to the recipient’s concern regarding the graft size. The technique of donor and recipient evaluation has been described elsewhere (8). The liver volume calculations were done according to CT volumetric analysis. The recipient standard liver volume (SLV) was calculated according to the Urita formula (9). The graft weight was taken on the back table after flushing the graft with preservation solution.

**Study groups**

Fifty patients undergoing LDLT with GRWR<0.8 were identified and divided into Group 1 (n=28): 2 HA stumps with 1 HA reconstruction and Group 2 (n=22): 2 HA stumps with reconstruction of 2 HAs.

**Operative techniques**

The techniques of donor heptectomy and recipient heptectomy have been described in detail elsewhere (10, 11). In the donor, all the arterial structures were carefully dissected and preserved. The proper HA was exposed up to the bifurcation of the left (or middle HA) and the right HA. The plane of division of the HA was determined by the length and size of the artery, its relation with the cutting plane of the liver and the position of the arteries. Before division of the arteries, an intra-operative Doppler ultrasound (DUS) was done to confirm the vascular anatomy.

**HA reconstruction**

The decision regarding the reconstruction of single or multiple HAs was made depending on the pre-operative radiological and intraoperative assessments. Before transection of the liver parenchyma in the donor, an intra-operative Doppler ultrasound (Acuson, Mountain View, Colorado) was done to confirm the vascular anatomy.

In grafts with multiple arteries, intra-hepatic arterial flow was assessed, after temporary clamping of individual artery and checking for the intra-arterial communications.

In the recipient, during the graft implantation, after reconstruction of the thicker HA, back-bleeding from the thinner arterial branch was assessed and also Doppler arterial flow signals to all the liver segments were confirmed. If any of these findings suggested incomplete liver graft arterial perfusion, both the arterial branches would be reconstructed. There was no selection bias with regards to the surgical expertise or the techniques and all the reconstructions were done by the same experienced micro-vascular surgeon and the details of it have been already published elsewhere (12). Also, intra-operative DUS was used to confirm the patency of the reconstructed HV and portal vein by determining the waveforms, velocity and resistive index of the vessels. The arteries used in the recipients for reconstruction are shown in Table 1.

**Portal vein flow**
Portal vein flow was assessed by intra-operative DUS and was calculated as flow per minute per 100 gram of liver. If flow was found to be more than 250ml/min/100gm, splenic artery ligation was done to reduce excessive portal flow.

Post-operative care and follow-up

In the recipients, routine DUS was done post liver transplantation to determine adequate blood flow and velocities in the reconstructed arteries and veins. A diagnosis of vascular stenosis or thrombosis was made initially by DUS and then confirmed on 3-dimensional CTA.

Assessment of the outcomes

The outcomes post transplantation were assessed by graft loss, biochemical markers of hepatocyte injury (aspartate amino transferase and alanine amino transferase) and liver function (bilirubin and international normalized ratio; INR). Long-term outcomes were assessed with respect to patient and graft survival.

Small-for-size syndrome (SFSS)

Graft dysfunction was defined according to Dahm et al., as presence of two of the following on 3 consecutive days: bilirubin >100 μmoles/L, prothrombin time INR >2 and encephalopathy grade 3 or 4 in absence of any technical, immunological or infectious cause (13).

Statistical analysis

The cumulative overall survival rates and the graft-dysfunction-free survival rates were calculated using Kaplan Meier methods with the difference evaluated using Log Rank test. Paired t-test was used to analyze the effect of portal flow modulation. To compare frequencies between the 2 groups, we used the Chi-square test.

Univariate analysis was done using the Kaplan Meier method and compared using Log Rank test. Statistical significance was defined as p<0.05. All statistics were performed using SPSS version 16.0 (SPSS Inc., Chicago, IL, USA).

RESULTS

Donors and grafts

The mean donor age was 54 (50-57) years. There were 5 male and 35 female donors. All the donors recovered uneventfully and none of them required re-operation. The donor average hospital stay was 7.2 days (range, 5-10). Two donors had minimal bile leakage which was managed conservatively. No surgery was aborted due to donor-related factors.

The mean measured graft weight on the back table, post infusion of preservation solution, was 572.5 ± 116 grams. The mean actual GRWR across the study population was 0.72 ± 0.06. The median % Standard Liver Volume (SLV) was 42 ± 3.7%. The demographic and the operative data of the 3 groups are shown in Tables 2 and 3. The groups were comparable in all respects except for the duration for surgery which was longer in Group 2 (p=0.038). This could be due to the extra time required for second HA reconstruction in the recipient.

Portal flow hemodynamics

The upper limit of portal vein flow rate (PVFR) regarded as safe cutoff was 250ml/min/100gm. Portal flow modulation was done if the flow was greater than this value. Splenic artery ligation was done in 4 cases and splenectomy was done in 5 cases. The median PVFR before modulation was 272ml/min/100gm and post modulation it was 190ml/min/100gm. The portal vein flow decreased significantly (p=0.000) post intervention. Figure 1. All the liver grafts appeared well perfused post implantation and had good arterial, portal and hepatic venous flows as assessed by intra-operative Doppler ultrasound.

Survival outcomes

The median period of follow-up was 13 months (range, 1-48). There was no case of 30-day in-hospital mortality in any of the 2 groups. Also, there was no incidence of graft loss or primary non-function of any graft.

SFSS

After strict application of the definition of SFSS as described by Dahm et al., (13), there were a total of 4 cases in Group 1 and 2 cases in Group 2. The incidence of SFSS was comparable among the groups (p=0.418). Figure 2. However, all these patients had an uneventful recovery. The graft regeneration was adequate in all the other recipients since the synthetic function of the liver had recovered by 1 month post transplantation and the clinical conditions of the patients were good. The changes in the liver enzymes, bilirubin and international normalized ratio are shown in Figures 3, 4, 5 and 6. It is to be noted that all the enzyme levels returned to normal by 4 weeks post transplantation.
On univariate analysis, only a portal vein flow rate of >200ml/min/100gm of liver graft was found to be a risk factor for graft dysfunction; p=0.000. Further multivariate analysis was not done as only a single factor was found to be significant on univariate analysis. Table 4.

Other complications. The incidence of biliary strictures was comparable between Group 1(n=2) and Group 2 (n=0), p=0.803, within 6 months post transplantation.

Also there were 4 cases of bile leakage from the cut surface of liver (Group 1: 2 cases and Group 2: 2 cases). All these cases were managed non-surgically. There were 3 cases of acute rejections seen 2 in Group 1 and 1 in Group 2. The incidence of hepatic artery thrombosis in Group 1 (n=1) and Group 2 (n=0) was comparable (p=0.498). These cases were managed by early re-exploration and re-do arterial anastomosis with the same artery after trimming it.

Figure 1
Portal flow rate changes post modulation (paired t test; p=0.000 and 95%CI: 57.64-95.87)

Figure 2
Graft dysfunction free survival was comparable among the three 2 groups (p=0.418).

Figure 3
Post-transplantation serum bilirubin levels.
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Figure 4
Post-transplantation Prothrombin INR levels.

Figure 5
Post-transplantation serum amino alanine transferase levels.

Figure 6
Post-transplantation amino aspartate transferase levels.

Table 1
Recipient hepatic arteries (HA) used for reconstruction in LDLT.

<table>
<thead>
<tr>
<th>Groups</th>
<th>Size of recipient HA</th>
<th>Number of arteries</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>LHA</td>
<td>20</td>
</tr>
<tr>
<td></td>
<td>RHA</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>Branch of RHA</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>RHA</td>
<td>13</td>
</tr>
<tr>
<td>2</td>
<td>LHA</td>
<td>30</td>
</tr>
<tr>
<td></td>
<td>PHA</td>
<td>1</td>
</tr>
</tbody>
</table>

HA: hepatic artery, LDLT: living donor liver transplantation, LHA: left hepatic artery, RHA: right hepatic artery, PHA: proper hepatic artery.

Table 2
Demographic and clinical data

<table>
<thead>
<tr>
<th>Category</th>
<th>Group 1 (n=28)</th>
<th>Group 2 (n=22)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Donor age (yrs)</td>
<td>55 (4.3)</td>
<td>27 (5.1)</td>
<td>0.017</td>
</tr>
<tr>
<td>Recipient age (yrs)</td>
<td>53 (5.3)</td>
<td>82 (6.0)</td>
<td>0.000</td>
</tr>
<tr>
<td>Sex (M:F)</td>
<td>21:1</td>
<td>18:4</td>
<td>0.587</td>
</tr>
<tr>
<td>Child Pugh score</td>
<td>7 (2.5)</td>
<td>8 (2.8)</td>
<td>0.778</td>
</tr>
<tr>
<td>MELD</td>
<td>10 (2.5)</td>
<td>12 (5.6)</td>
<td>0.777</td>
</tr>
<tr>
<td>SCV (%)</td>
<td>42.8 (3.1)</td>
<td>40.2 (3.2)</td>
<td>0.222</td>
</tr>
<tr>
<td>Splenic size (mm)</td>
<td>616 (457)</td>
<td>763 (359)</td>
<td>0.474</td>
</tr>
<tr>
<td>Graft (right: left)</td>
<td>11:17</td>
<td>13:9</td>
<td>0.184</td>
</tr>
<tr>
<td>Diagnosis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HCV</td>
<td>2</td>
<td>3</td>
<td>-</td>
</tr>
<tr>
<td>HBV</td>
<td>6</td>
<td>3</td>
<td>-</td>
</tr>
<tr>
<td>HCV and HCC</td>
<td>14</td>
<td>9</td>
<td>-</td>
</tr>
<tr>
<td>HBV and HCC</td>
<td>4</td>
<td>2</td>
<td>-</td>
</tr>
<tr>
<td>Others</td>
<td>3</td>
<td>5</td>
<td>-</td>
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</tbody>
</table>

Data is expressed as mean ± SD.

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Table 3
Operative details of the recipients

<table>
<thead>
<tr>
<th>Category</th>
<th>Group 1</th>
<th>Group 2</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Graft HA size (mm)</td>
<td>2.5 (4.4)</td>
<td>2.4 (4.4)</td>
<td>0.239</td>
</tr>
<tr>
<td>Cardiac ischemic time (min)</td>
<td>40 (4.4)</td>
<td>37 (11)</td>
<td>0.441</td>
</tr>
<tr>
<td>Warm ischemic time (min)</td>
<td>37 (5.3)</td>
<td>56 (3.4)</td>
<td>0.083</td>
</tr>
<tr>
<td>Duration of surgery (min)</td>
<td>534 (76)</td>
<td>857 (158)</td>
<td>0.038</td>
</tr>
<tr>
<td>Blood loss (ml)</td>
<td>5520 (2120)</td>
<td>9670 (1000)</td>
<td>0.320</td>
</tr>
<tr>
<td>GRWR</td>
<td>0.7 (0.05)</td>
<td>0.7 (0.07)</td>
<td>0.813</td>
</tr>
<tr>
<td>Graft weight (gm)</td>
<td>611 (123)</td>
<td>523 (99)</td>
<td>0.386</td>
</tr>
<tr>
<td>PVF (ml/min/100gm)</td>
<td>186 (60.4)</td>
<td>204 (62.7)</td>
<td>0.284</td>
</tr>
<tr>
<td>Portal flow modulation (SAL: Splenectomy)</td>
<td>2.3</td>
<td>3.1</td>
<td>0.076</td>
</tr>
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</table>

Table 4
Risk factors for graft dysfunction

<table>
<thead>
<tr>
<th>Category</th>
<th>Univariate analysis p-value</th>
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</thead>
<tbody>
<tr>
<td>Splenomegaly</td>
<td>0.891</td>
</tr>
<tr>
<td>Type of graft</td>
<td>0.792</td>
</tr>
<tr>
<td>PVF &gt;2000 ml/min/100gm</td>
<td>0.890</td>
</tr>
<tr>
<td>MELD</td>
<td>0.336</td>
</tr>
<tr>
<td>Cold ischemic time</td>
<td>0.161</td>
</tr>
<tr>
<td>Warm ischemic time</td>
<td>0.182</td>
</tr>
<tr>
<td>Duration of surgery</td>
<td>0.276</td>
</tr>
<tr>
<td>Blood loss</td>
<td>0.270</td>
</tr>
<tr>
<td>Non-reconstructed artery</td>
<td>0.920</td>
</tr>
<tr>
<td>GRWR</td>
<td>0.725</td>
</tr>
<tr>
<td>CTPA</td>
<td>0.762</td>
</tr>
<tr>
<td>Graft HA size (mm)</td>
<td>0.763</td>
</tr>
<tr>
<td>Hepatic artery thrombosis</td>
<td>0.199</td>
</tr>
</tbody>
</table>

DISCUSSION

This study illustrates that reconstructing a single HA in a liver graft having dual HA stumps and low GRWR has no impact on post-transplantation incidence of SFSS in LDLT with SFS liver graft.

One of the landmark studies demonstrating the impact of partial liver graft weight on post-transplantation outcomes was done by Kuichi et al. They published the results in a large study population showing that grafts with GRWR <1 had statistically inferior outcomes as compared to those with GRWR >1 (1). Recently, grafts with GRWR <0.8 have been called small for size grafts (SFSG) and are cautioned to be at an increased risk of developing SFSS. This is based on the results extrapolated from animal studies demonstrating progressive damage linked to portal hyperperfusion leading to sinusoidal congestion, disruption of sinusoidal lining cells and eventually collapse of the space of Disse and cholestasis (14-18). However, some studies have reported excellent survival in recipients undergoing LDLT with liver grafts having a GRWR of <0.8 with excellent outcomes by creating hemiporto-caval shunts (19, 20), splenic artery ligation or splenectomy (19, 21-24). In our study population, we encountered SFSS in 7/54 (13%) of the cases. However, none of them suffered from graft loss or in-hospital 30-day mortality.

We followed the protocol of portal flow modulation in case the PVFR was >250ml/min/100gm. Splenic artery ligation or splenectomy effectively reduced the PVFR to <250ml/min/100gm.

The reciprocal hemodynamic relation between the portal vein flow and recipient hepatic artery flow post transplantation has been described previously (25). It was shown that the mean portal contribution to graft blood flow was 94% and the mean portal-to-arterial ratio was 29. They also suggested that performing splenic artery ligation at the root of the artery allowed an increase in recipient arterial flow and a decrease in portal vein flow to the graft. Thus it was interesting to see what impact would reconstructing only single HA would have on the incidence of SFSS. All the HAs were reconstructed using microsurgical techniques resulting in better outcomes as already described elsewhere by our group (12).

Studies have been done in the past demonstrating the outcomes of reconstructing a single HA with respect to incidence of biliary strictures in LDLT (26, 27). However, none of these studies included grafts with a GRWR of <0.8 and they did not study the incidence of graft dysfunction. One of the most common causes of SFSS is portal hyperperfusion (28). In most of the series, a PVFR >250 ml/min/100gm is regarded as risk factor for development of SFSS (29). In our study, a PVFR >200 ml/min/100gm was identified as a risk factor for the development of SFSS.

It is generally accepted that the recipient’s general condition also influences the occurrence of SFSS (30-33). In our study, most of the recipients were having a better clinical condition being mostly Child A/B with lower median MELD score.

It is a well-known fact that graft weight may be overestimated in about 20% with respect to volumetric...
measurements (34). This has to be taken in to consideration when selecting donors for LDLT.

In conclusion, the problem of presence of multiple HAs in the SFSG graft can be dealt with by reconstructing a single HA, after confirming the presence of intra-hepatic arterial communications. This offers as a safe and feasible option in LDLT with SFSG and does not have an impact on the incidence of SFSS post transplantation.

References
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