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Living related adult-to-adult liver transplantation: meeting the donor shortage

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Abstract

Experience in the Cromwell Hospital London, Adult-to-Adult Living Donor Liver Transplantation programme is described with particular reference to the results obtained in the first five recipients. The first two of these received a left lobe graft and the remaining three a right lobe graft. Three sons/daughters, and two siblings were the donors. Four of the five recipients survived and did well. The one recipient who died was a complicated retransplant procedure. The donors showed rapid recovery of liver function with normal tests by the 10th day and with evidence of regeneration on follow-up CT volume evaluation. The value of the procedure for patients who have little chance of obtaining a cadaver organ is undoubted, but critical assessment of the recipient's clinical state is essential if success is to be obtained with a small graft and at all times the safety of the donor must remain of paramount concern, as reports to date indicate instances of donor death in adult programme.

Keywords: Adult-to-adult; Liver transplantation; Donor shortage

1. Introduction

Experience to date with the adult-to-adult Living Related Liver Transplantation (LRLT) programme at the Cromwell Hospital, London, has convinced me of the place that this technique could have in ameliorating the worsening cadaver donor organ shortage around the world. The advantages to the recipient in having excellent graft function in the immediate post-operative period are also self evident (Table 1). But, I am also increasingly aware of the considerable responsibilities placed on the physician and indeed on the whole transplant team when the graft is obtained in this way from a healthy relative or from an unrelated spouse or partner. With the donor prepared to undergo a major surgical procedure with 5–6 days minimum stay in hospital, every effort must be made to ensure that the risks for the donor are minimised and that the chances of a worthwhile outcome for the recipient are high.

The series at the Cromwell Hospital (CH) is

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specifically directed towards the needs of overseas patients, as in the UK they have no priority for a cadaver organ graft and can only get transplanted if there is no NHS patient or EEC entitled case suitable for the graft. The increasing size of the waiting list in this, as in other countries, and the plateau in the number of organ donations, means that for an overseas patient the wait for a cadaver organ is of the order of 1–2 years, or even longer for blood group O recipients. Rarely does the patient's condition allow them to wait this long and the experience of seeing these people dying on the waiting list makes the ethics of the procedure, for me, relatively simple. Although zero donor morbidity and uniform recipient survival may not be universally obtainable, every effort must be made to get as near as possible to those endpoints (Marcos, 2000). This means that the donor has to be fully investigated to exclude any adverse factors in their ability to make and survive the donation and that the surgical and anaesthetic team have to have expertise in liver resections and split liver techniques (and preferably of LRLT in children).

The programme was initially based on the procedures developed by Kawasaki and his group in Shinshu University, Japan. Although I had previously been involved in the LRLT programme for paediatric recipients at King's College Hospital, it was the presentation of Dr. Kawasaki at the Asian Pacific Congress of Liver Disease at Perth in February 1998 which alerted me to the potential of this procedure for adults requiring liver transplantation. In Kawasaki's series, there had been a progression over the years from the use of left lateral segments in infants to the treatment of larger children and then young adults, increasing the size of the graft to take the whole of the left lobe. In our later cases, in preference for reasons that will be discussed, the right lobe has been used to obtain a larger mass of functioning graft as pioneered by H.T. Fan's group in Hong Kong.

2. Assessment of donor

This can conveniently be considered in three stages (Table 2). The first is concerned with establishment of blood group compatibility and of the general medical and liver suitability. In ensuring this, a considerable range of blood tests and virological screening (particularly hepatitis B and C), along with specific cardio-respiratory and renal assessment are required. Formal psychological assessment is also helpful ensuring that the donor has motivation and understanding and full knowledge of his/her past medical history is essential. At least part of the assessment can be carried out in the donor's own country so that the donor arrives with at least some knowledge of what the procedure entails for them and major contraindications to donation have been excluded. Ultrasound examination of the liver is useful in giving some indication of the size of left and right lobes, donation being too dangerous if anatomical variation has resulted in one or other lobe being unduly small. The finding of any abnormality suggestive of pre-existing liver disease would also exclude donation because of likely impairment of regenerative ability. A degree of steatosis is acceptable but probably no more than an estimated 30% of overall liver mass. In such instances liver biopsy assessment may also be required.

Table 1
Advantages of living-donor liver transplantation

1.	Optimal timing of transplant before development in recipient of severe/irreversible complications.
2.	Short ischaemia time and lack of other adverse factors, as with cadaveric donors, means excellent initial function of graft and more rapid recovery of recipient; possible less acute rejection.

Table 2
Stages in assessment of potential donor

Stage 1	Establishment of blood group compatibility, general medical and liver suitability (including US), initial consent, HLA typing.
Stage 2	Determination of liver lobe sizes (CT or MRI) and other investigations of anatomy. Hepatic vascular supply (angiography) and biliary tract anatomy (MRCP screening).
Stage 3	Final consideration of results by surgical, anaesthetic and medical team; second consent procedure.

Table 3
Calculation of standard liver volume

SLV ml = $706.2 \times$ body surface area $(m^2) + 2.4$ or $6.293 \times$ body weight $(kg)^{0.426} \times$ height $(cm)^{0.682}$

Invasive procedures become necessary in the second stage. Hepatic angiography is an essential investigation in planning the donor resection, for the vascular structure has to be divided in such a way that results in a well vascularised graft but still preserves the inflow to the remnant liver. A right lobe resection represents approximately 60% of liver mass and overt ischaemia or even sub-optimal perfusion of the left lobe could impair regeneration. Preservation of the vasculature to segment 4 is mandatory. Either CT or MRI can be used for volumetric imaging to determine absolute sizes of left and right lobes and are related to calculated standard liver volume (Table 3) or body weight of the recipient (Urata et al., 1995). Only 60% of donors have normal biliary anatomy on either the right or left and although anomalous anatomy is not often a contraindication of liver donation, knowledge of it is essential in determining the line of resection and the best anastomosis of the bile ducts. The degree of definition with non-invasive studies with MRI is rarely as good as can be obtained by intra-operative cholangiography, which remains the best way of properly evaluating the donor biliary tract. Pre-operative ERCP carries the risk of pancreatitis as occurred in one of our donors and is best avoided.

The third stage is concerned with a final consideration of all the results and anatomical findings relevant to which lobe is used as well as the donor's condition generally and psychological suitability. Preferably this is done at a joint meeting of all those concerned with the surgery and after-care, following which the donor's final consent to the procedure is sought.

3. Initial patients and lessons learned

Details of the first four patients in the series who had been transplanted by the time of the Congress in January 2000 and post-resection data for the donors are given in Tables 4 and 5. The initial recipient, a 43-year-old lady from Iran with end-stage HCV cirrhosis, received left lobe segments 2 and 3 along with part of segment 4 from her daughter aged 20 years. Recovery of the donor was uneventful with some prolongation of INR and minimal elevation in serum bilirubin over the first 48 h post-operatively. Values had returned to normal by time of discharge from hospital on the 7th day. Her mother's recovery was relatively slow with leakage of ascitic fluid and on day 7 a haematemesis. The latter was attributed to portal venous congestion consequent on excessive blood flow through the small graft, liver biopsy showing areas of congestion and necrosis as well as florid areas of regeneration.

Table 4
Cromwell Hospital LRLT programme: adult-to-adult

Case	Transplant indication	Donor and lobe used	Complications	Liver volume 6 weeks (standard liver volume)
1	HCV cirrhosis (aged 43)	Daughter (aged 20) left 2/3 & pt 4	GI bleed day 7, cholestasis	1040 (1067)
2	HCV recurrence (aged 57)	Son (aged 24) left 2/3 & 4	Occl. acc. art. Segment 4, day 7, cadaveric retransplant	– (1062)
3	HBV cirrhosis (aged 42)	Brother (aged 37) right lobe	None	1291 (1203)
4	Crypt. cirrhosis (aged 45)	Daughter (aged 18) right lobe	None	1137 (1344)

Table 5
Serum bilirubin and liver volume (CT) of donor after donation

	Prothrombin time (Max INR)	Serum bilirubin (μmol/l)	Liver volume	
			Pre	4–6 weeks
1 (Segments 2, 3 pt 4)	1.5	22	1285	970
2 (Segments 2,3 and 4)	1.7	68	1299	955
3 (Right lobe)	2.0	92	1492	1332
4 (Right lobe)	2.3	21	1197	930

The second case was a man aged 57 years from Israel requiring re-transplantation on account of recurrent end stage HCV disease of a cadaver transplant carried out in 1985. The donor was his son and the whole of the left lobe was used to obtain a larger functioning graft. Revascularisation was complicated by the presence of a small accessory artery to segment 4 and although initially the recipient did well, on day 4 the serum transaminases became markedly elevated and angiography showed lack of perfusion to that area. The graft was removed 2 days later—when the right lobe of a cadaver split liver procedure unexpectedly became available—and showed large infarcts involving the whole of segment 4 and adjacent areas of segments 2 and 3. Sadly, the patient's respiratory function deteriorated with repeated infections and he finally succumbed from multi-organ failure and died 5 weeks later. Despite the considerable psychological trauma attendant on his father's demise, the son made a good recovery and proffered the view before his departure home that he felt justified in having done everything possible to save his father's life.

Following this experience, and with the knowledge that right lobe donation was increasingly the preferred approach in other programmes, it was decided for the third recipient, a 42-year-old male, to use the right lobe of his donor brother. Clinical recovery and biochemical improvement in the recipient was rapid and the donor's recovery was also uneventful. Although he showed marked abnormalities in serum bilirubin and INR during the first 48 h post-resection, normal function had been regained by the 10th day. The recovery of the fourth recipient—a man of 45 years with end-stage HCV-related cirrhosis—was similarly rapid and his donor daughter showed only minimal derangement in liver function tests following the right lobe resection.

Since that time, a further three patients have been successfully transplanted with right lobe donations—case 5 from a brother, case 6 from a daughter, and case 7 from a brother—without complications to either party. Two other LRLTs were aborted in the final stages. In one, this was because the recipient developed, 6 h prior to going to theatre, rapidly deteriorating pulmonary oxygenation as a result of chest infection and septicaemia. The other was found at laparotomy to have tumour (HCC) extension beyond the liver that had not been shown in pre-operative imaging.

4. Right versus left lobe donation and size of graft

This is a subject of an excellent review by Marcos based on experience in the University of Virginia programme of 41 right lobe adult LRLTs (Marcos et al., 1999; Marcos, 2000). At the meeting of the Society of Transplant Physicians and Surgeons in Chicago (May, 2000), the number of adult LRLT utilising the right lobe numbered over 250 carried out in 32 centres, the largest series at Mount Sinai Hospital New York comprising 48 procedures. The technical advantages of the right lobe over the left include a greater calibre of vessels so that microscopic anastomosis is not required. Also, the right graft can be placed in the natural position in the right upper quadrant of the recipient and complications resulting from graft malposition with the kinking of vessels does

not occur. The risk to the donor of the more extensive resection may be more perceived than real, provided that the circulation to segment 4 (a significant part of which can come from the right hepatic artery) is carefully protected during the right lobectomy. Post-operative MRIs in Marcos' series showed that segment 4 contributed significantly to the restoration of donor hepatic mass. The 41 donors in his series were left with a mean of 37% of their initial cell mass but no serious complications occurred. Rapid regeneration was observed on MRI within 14 days. On the clinical course of the 41 recipients, Marcos reported that they appeared to be readmitted less frequently than cadaver transplants and that there were no instances of primary non-function. Acute rejection had also not been seen, which is consistent with other reports of immunological benefit in adult-to-adult LRLT, although this has not been shown for paediatric LRLT.

The majority of the 41 recipients were UNOS IIB. Two were status I (acute liver failure) and six were UNOS status IIA. The three recipients who died came from the latter group, as did the one unsuccessful case in our series to date. It is important that the donor sees a successful outcome to their extraordinarily generous sacrifice, and UNOS IIA cases with severe hepatic decompensation should preferably be treated by a full size cadaver graft. The fact that UNOS I cases usually do not have long-standing disturbances to cardiovascular, kidney and other organ function as well as their urgent need for a transplant make them, in my view, a suitable group of patients to be considered for LRLT.

This raises the question of just how much liver function is required of the graft in the correction of severe metabolic abnormalities and maintaining life. Liver segments representing as little as 20% of standard liver mass have been transplanted and have functioned well, nevertheless the risk for graft loss increases with decreasing size. Some centres use graft to recipient body weight (GRBW) ratios and others graft weights as a percentage of calculated standard liver mass of the recipient. There is an excellent correlation between the two values and a GRBW ratio of 1% approximates to 50% of standard liver mass. Experience shows that grafts that represent less than 40–50% of standard liver mass (GRBW < 0.8–1%) consistently show delayed functional recovery. In one large series of 276 LDLTs, a statistically significant association between graft loss and GRBW of less than 1% was demonstrated, although only one graft was lost acutely and infectious complications appeared to be the commonest cause of graft loss and recipient mortality (Kiuchi et al., 1999).

However, Kawasaki's group, already referred to, have reported satisfactory outcome even in acute liver failure with left lobe donations, provided the ratio of graft volume to standard liver volume of the recipient was greater or equal to 35% (Miwa et al., 1999). Thirteen of 14 patients (including 4 adults) with acute liver failure from a series of 106 LRLTs carried out during the years 1990–1999, are alive. Normalisation of the serum bilirubin occurred within 3–5 days and the coagulation profile from 4–7 days. Graft volumes as determined by CT measured 231–625 ml and represented either left lobe segments, the complete left lobe and in one case additionally the left part of the caudate lobe. These patients had been treated for 1–2 weeks with intensive liver support based on repeated plasmapheresis and haemadiafiltration and it is likely that some control of the metabolic derangements had been achieved. The fact that they had already survived so long perhaps also means they did not represent the most severe instances of acute liver failure.

A 'high urgency' situation with severe liver decompensation in chronic liver disease and/or acute liver failure was present in 14 of the 25 patients who underwent LRLT recently reported by the Hong Kong group. The grafts composed ten left lateral segments, six left lobes and nine extended right lobes. The survival rate was 95% when the ratio of graft weight to standard liver volume of recipient was $> 40\%$. With a ratio of $< 40\%$, the serum bilirubin was higher and prothrombin time more prolonged post-transplant and survival was only 40% (Lo et al., 1999).

Whether or not the recipient will survive with a graft of minimal size is likely also to depend on the pre-operative state of the recipient and any adverse influences on the graft during the trans-

plant and over the first post-operative week, which could delay regeneration of the liver. Although the safety of the donor must to some extent depend on the amount of liver left behind, damage to the biliary system or vascular supply of the remaining lobe will be the most important factor. Regeneration from the remnant, whether small or large, should occur over the first 4 weeks.

5. Donor safety and likely development of LRLT

At the International Liver Transplant Society meeting in Pittsburgh during August 1999 it was clear that this procedure was going to be taken up widely throughout the USA as has indeed happened. Experience in Europe was at that time more limited although Christoph Broelsch in Essen had carried out 28 adult procedures based on his very considerable experience of living related donation for infants and children. At that meeting there was also much concern over reports of a recent donor death in North Carolina. The only published instance of donor death—from a pulmonary embolism in a woman who was overweight and on contraceptive hormones—was from Hamburg many years previously. But in an editorial entitled 'Whither living donor liver transplantation?' and published in the November issue of *Liver Transplantation and Surgery*, Russell Strong (1999), drew attention to a greater number of deaths: "I am aware of six donor deaths but to date only one death has been reported in the medical literature. It is understandable that transplant programmes are reluctant to advertise a donor death but by not doing so clinicians are deprived of essential information to properly inform potential donors. It makes a mockery of informed consent and jeopardises a decision by the prospective donor… The informed donor may be the best qualified person to make the final decision… Teams embarking on adult-to-adult transplantation using right hemi-liver cannot plead ignorance of significant risk to the donor and must accept a heavy burden of responsibility for the advice to the family and outcome of the procedure."

This was indeed a most timely editorial and undoubtedly will reign back enthusiasm and make transplant teams think very carefully about proceeding along the pathway of LRLT, particularly when based on use of the right hemi-liver. Those seeking consent for a donation will be bounden to give this extra information on the number of donor deaths. But one does need to know the cause of the fatalities and how avoidable they were. It has been suggested that there should be a register of living donations to gain information on long-term outcome as well and, in my view, this should be a compulsory part of national transplant statistics and audit.

Nevertheless, it is likely that the families will continue to want to donate, even when given the further information with respect to donor fatality, if there is no other chance of their loved one obtaining a donor organ. LRLT will therefore find greatest favour in countries where there is a long waiting list for cadaver organs, as in the USA and many parts of Europe (Table 6), quite apart from being used in countries where cultural or legal restrictions have hindered the acceptance of brain death criteria and cadaver organ donation for transplantation. In the UK the waiting list is still quite small, which is at least partly related to the lower frequency of liver disease as compared with other countries in Europe. Cur-

Table 6
Evolution of the waiting list for liver transplant 1995–1997

	ET[a]	EFG (France)	NIT (North Italy)	ONT (Spain)	UKTSSA (UK and Ireland)	UNOS (USA)
1995	263	316	244	216	153	5691
1996	327	237	363	297	195	7467
1997	374	247	433	289	196	9637

[a] Eurotransplant: Germany, Austria, Belgium, Luxemburg, The Netherlands.

Table 7
Organ donors and liver transplants per million population (1998)

	Organ donors	Liver transplants
Spain	31.5	22.7
France	16.9	11.8
Eurotransplant[a]	14.4	9.4
UK and Ireland	13.5	11.0
Italy	12.3	9.5
USA	21.6	16.6

[a] Germany, Austria, Belgium, Luxemburg, The Netherlands.

rently, there is considerable variation within Europe in the current rates for cadaver organ donation. In Spain, the rate is almost double that of the UK allowing almost twice as many transplants to be carried out (Table 7). This is as a result of the introduction of an efficient donor retrieval coordinator system as well as statutory requirements on the hospital to maximising cadaver organ donation quite apart from the presumed consent legislation which is in place. Only after every effort to enhance the number of transplants carried out from cadaver organs can the true number of patients that may require treatment by LRLT—in relation to their likely waiting time on the waiting list—be estimated.

6. Conclusion

1. Adult-to-adult LRLT is a procedure which can be dramatically successful for both recipient and donor. The period of hospitalisation for the recipient because of excellent graft function is shorter, and rapid recovery of the donor's liver to the previous size is documented after both right and left hemi-liver donation.
2. Knowledge of higher mortality figures for the donor is likely to slow but not stop the otherwise rapidly increasing take up of this type of transplantation for the adult. It is important that full information on living related donors is recorded in National transplant registers and that teams carrying out the procedures have the considerable expertise necessary for the procedure along with all necessary laboratory and other hospital facilities.
3. Cadaver organ donor rates need to be maximised worldwide with critical assessment of recipient need so that waiting times for a cadaver organ can be reduced, and with this the pressure on adult-to-adult LRLT programmes.

References

Kiuchi, T., Kasahara, M., Uryuhara, K., Inomata, Y., Uemoto, S., Asonuma, K., Egawa, H., Fujita, S., Hayashi, M., Tanaka, K., 1999. Impact of graft size mismatching on graft prognosis in liver transplantation from living donors. Transplantation 67, 321–327.

Lo, C.M., Fan, S.T., Liu, C.L., Chan, J.K., Lam, B.K., Lau, G.K., Wei, W.I., Wong, J., 1999. Minimum graft size for successful living donor liver transplantation. Transplantation 68, 1112–1116.

Marcos, A., Fisher, R.A., Ham, J.M., Shiffman, M.L., Sanyal, A.A.J., Luketic, V.A., Sterling, R.K., Posner, M.P., 1999. Right lobe living donor liver transplantation. Transplantation 68, 798–803.

Marcos, A., 2000. Right lobe living donor liver transplantation: A review. Liver Transpl. 6, 3–20.

Miwa, S., Hashikura, Y., Mita, A., Kubota, T., Chisuwa, H., Nakazawa, Y., Ikegami, T., Terada, M., Miyagawa, S., Kawasaki, S., 1999. Living-related liver transplantation for patients with fulminant and subfulminant hepatic failure. Hepatology 30, 1521–1526.

Strong, R., 1999. Whither living donor liver transplantation? Liver Transpl. Surg. 5, 536–538.

Urata, K., Kawasaki, S., Matsunami, H., Hashikura, Y., Ikegami, T., Ishizone, S., Momose, Y., Komiyama, A., Makuuchi, M., 1995. Calculation of child and adult standard liver volume for liver transplantation. Hepatology 21, 1317–1321.