Technical aspects of liver transplantation
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CHAPTER 9

SUMMARY, CONCLUSIONS AND RECOMMENDATIONS
SUMMARY

This thesis concerns selected technical aspects of the complex surgical procedure to transplant a liver graft from deceased donors to a recipient with a liver failure. In Chapter 1 the complexity of the liver transplantation is explained and the aims and outlines of the thesis are presented. Chapter 2 gives an overview over the technical developments of the transplant procedure, which have taken place during the past four decades after the first liver transplantation in humans. The available evidence is presented regarding the contribution of the techniques to the improved outcome. Chapter 3 presents the results of the first reported open comparison between the outcomes of two liver transplant centers. We analyzed the differences in the outcome of two European liver transplant centers differing in case volume and experience. The first was the Transplantation and Surgical Clinic, Semmelweis University, Budapest, Hungary (SEB) and the second the University Medical Center Groningen, Groningen, The Netherlands (UMCG). We investigated if such differences could be explained. The 1-, 3- and 5-year patient survival in the UMCG was 86%, 80%, and 77% compared with 65%, 56%, and 55% in SEB. Graft survival at the same time points was 79%, 71%, and 66% in the UMCG and 62%, 55%, and 53% in SEB. Significant differences were present regarding the donor and recipient age, diagnosis mix, disease severity and operation variables, preoperative transfusion rate, vascular complications, postoperative infection rate, and need for renal replacement. To determine factors correlating with survival, a separate uni- and multivariate analysis was performed in each center individually, between study parameters and patient survival. In both centers, perioperative red blood cell (RBC) transfusion rate was a significant predictor for patient survival. The difference in blood loss can be explained by different operation techniques and shorter operation time in SEB, with consequently less time spent on hemostasis. It was jointly concluded that measures to reduce blood loss by adapting the operation technique might lead to improved survival and reduced morbidity. As a result of this analysis measures have been taken in SEB to adapt the peri-operative protocols regarding hemostasis, prevention of HAT (low hematocrit and post operative thrombosis prophylaxis) and infection prevention. So far this has led to an improvement of one and two year patient survival after 2002 of 80 and 76%, respectively. Chapter 4 describes the results of our study comparing two techniques of liver transplantation, conventional and piggyback technique in terms of patient and graft
survival, operative parameters and postoperative complications. A consecutive series (1994–2000) of 167 adult primary OLT were analysed. Ninety-six patients had CON-OLT and 71 patients had PB-ES. In PB-ES group two revascularization protocols were used. In the first protocol reperfusion of the graft was performed first via the portal vein followed by the arterial anastomosis (PB-seq). In the second protocol the graft was reperfused simultaneously via portal vein and hepatic artery (PB-sim). One-, 3- and 5-yr patient survival in the CON-OLT and PB-ES groups were 90, 83 and 80%, and 83, 78 and 78%, respectively (p=ns). Graft survival at the same time points was 81, 73 and 69%, and 78, 69 and 65%, respectively (p=ns). Apart from the higher number of patients with cholangitis and sepsis in CON-OLT group, morbidity, retransplantation rate and post-operative liver and kidney function were not different between the two groups. The total operation time was not different between both groups (9.4 h in PB-ES vs. 10.0 h in CON-OLT), but in PB-ES group cold and warm ischaemia time (CIT and WIT), revascularization time (REVT), functional and anatomic anhepatic phases (FAHP and AAHP) were significantly shorter (8.9 h vs. 10.7 h, 54 min vs. 63 min, 82 min vs. 114 min, 118 min vs. 160 min and 87 min vs. 114 min, respectively, p < 0.05). RBC use in the PB-ES group was lower compared to the CON-OLT group (4.0 min vs. 10.0 units, p < 0.05). Except for WIT and REVT there were no differences in operative characteristics between PB-Sim and PB-Seq groups. The WIT was significantly longer in PB-Sim group compared with PB-Seq group (64 min vs. 50 min, p < 0.05); however REVT was significantly shorter in PB-Sim group (64 min vs. 97 min, p < 0.05). Results of this study show that both techniques are comparable in survival and morbidity; however PB-ES results in shorter AAHP, FAHP, REVT and WIT as well as less RBC use. In the PB-ES group there seems to be no advantage for any of the revascularization protocols.

As no consensus exists regarding the optimal reconstruction of the cavo-caval anastomosis in piggyback orthotopic liver transplantation (PBLT) our experiences with the technique of end-to-side caval anastomosis are described in Chapter 5. Outcome parameters were patient and graft survival and surgical complications. During the period 1995–2002 146 full-size PBLT in 137 adult patients were performed with ES cavo-cavostomy without the routine use of temporary portocaval shunt (TPCS). In 12 patients (8%) this technique was used for implantation of second or third grafts. Venovenous bypass was not used in any case and TPCS was performed only in eight patients (6%). One-, three- and five-years patient and graft survival were 84%, 79% and 75%, and 81%, 74% and 69%, respectively. The median number of intraoperative transfusion of packed red blood cells (RBC) was 2.0 (range 0–33) and 30% of the
patients (n=43) did not require any RBC transfusion. Surgical complications of various types were observed after 49 LT (34%) and none of the complications was specifically related to the technique of ES cavo-cavostomy. Our experience indicates that PB-LT with ES cavo-cavostomy is a safe procedure, can safely be performed without the routine use of a TPCS, has a very low risk of venous outflow obstruction and can also be used effectively during retransplantations.

Chapter 6 gives an overview about current techniques of revascularization in liver transplantation. Sequential revascularization allows a short WIT, which has been shown to be a clinically important determinant of outcome and initial hepatocellular function. Concerning postreperfusion liver injury there are no significant differences between initial arterial revascularization and initial portal revascularization. Also the more recently advocated method of retrograde reperfusion via the IVC seems to provide good postoperative liver function with a low incidence of initial graft dysfunction. However, data suggest that this method, similarly to IPR, carries a high risk of ITBL, probably because of lack of arterial flow to the bile ducts in the progressively rewarming graft, causing ischemic injury to the biliary epithelium. Although the aim of simultaneous arterial and portal reperfusion has been to prevent biliary complications, the available results are conflicting and not conclusive. Moreover, the prolongation of WIT and anhepatic phase associated with simultaneous reperfusion may have an overall negative impact on postoperative graft function.

With respect to the hemodynamic changes associated with graft reperfusion, IPR seems to offer a more favorable immediate perfusion, compared to IAR. However, IAR is associated with less increase in pulmonary artery pressure and may, therefore, be indicated in patients with a poor cardiopulmonary reserve. Apart from these general differences, the anatomical situation in an individual patient can make one technique preferable over the other. For example, in case of extensive portal vein thrombosis, it is sometimes safer to construct the arterial anastomosis first, securing blood flow to the liver and avoiding extra warm ischemia when thrombectomy of the portal vein (unexpectedly) has not resulted in optimal restoration of hepatic blood flow. Another aspect is that the portal vein anastomosis is usually technically easier and more straightforward than the arterial anastomosis. The latter is more prone for technical failure and sometimes requires more time and concentration.

The results of comparison of two reperfusion protocols, a sequential one with first portal vein reperfusion followed by arterial reperfusion and a simultaneous reperfusion protocol are presented in Chapter 7. The study population consisted of 102 adult
patients with primary full-size piggyback OLT transplanted between January 1998 and December 2001. In 71 patients (70%) the grafts were sequentially reperfused after completion of the portal vein anastomosis and subsequent arterial reconstruction was performed (SeqR group). In 31 patients (30%) the graft was reperfused simultaneously via the portal vein and hepatic artery (SimR group). Patient and graft survival at 1, 3, and 6 months and at 1 year did not differ between the SeqR group and the SimR group. The red blood cell (RBC) requirements were significantly higher in the SimR group (5.5 units; range 0-20) in comparison to the SeqR group (2 units; range 0-19) (p=0.02). Apart from a higher number of biliary anastomotic complications and abdominal bleeding complications in the SimR group in comparison to the SeqR group (13% vs. 2% and 19% vs. 6%, respectively; p= 0.06), morbidity was not different between the groups. No differences between the groups were observed regarding the incidence of primary nonfunction (PNF), intensive care unit stay, and acute rejection. This was also true for the severity of rejections. Postoperative recuperation of liver function was not different between the groups. In conclusion, no advantage of either of the 2 reperfusion protocols could be observed in this analysis, especially with respect to the incidence of ischemic type biliary lesions (ITBL).

Chapter 8 describes the results of liver transplantation in children with body weight below or equal to 10 kg transplanted with grafts from deceased donors. Between November 1982 and March 2006, 67 children with a BW of 10 kg or less had a primary liver transplantation from deceased donors in our unit. Overall one, three, five and ten-year primary patient and graft survival rates were 73%, 71%, 66%, 63% and 59%, 56%, 53%, and 48%, respectively. 24 of 67 (36%) children died and in 22 the first grafts failed and they were retransplanted (33%). Cox regression analysis revealed that a need for retransplantation and urgent transplantation were important predictors for patient survival (p=0.04 and p=0.001, respectively). To assess whether the need for retransplantation can be influenced, all study variables were compared between surviving grafts and failed grafts. Cox regression analysis showed that only D/R weight ratio proved to be independent predictor for graft survival (p=0.004). After comparison of graft survival with the long rank test according to different D/R weight ratios (3.0-7.0), the cut-off point for significantly different graft survival approached 4.0 The one, three, five and ten year graft survival for technical variant grafts with a D/R weight ratio below 4.0 was 85%, 68%, 68% and 68%, respectively compared to 44%, 38%, 38%, and 30%, respectively for grafts with a D/R weight ratio above 4.0 (p=0.02). In summary, patient survival in children with a body weight below or equal to 10 kg
is determined by urgent transplantation and the need for retransplantation. Graft loss and retransplantation in small children can be prevented by adequate size matching of donor and recipient whereby a D/R weight ratio below 4.0 seems to offer the favorable outcome.

**CONCLUSIONS AND RECOMMENDATIONS**

1. **Peri-operative transfusion rate in liver transplantation can be reduced by adaptations in surgical techniques.**

   One of the most important factors influencing peri-operative blood loss is surgical technique. Adaptation in surgical technique may lead to a decrease in transfusion rate with subsequent improvement of survival (Chapter 3). The piggyback technique offers reduction of blood loss during operation compared to the conventional technique (Chapter 3 and 4). Using this technique together with end-to-side caval anastomosis 1/3 of all adult liver transplantation can be performed without any peri-operative blood transfusions (Chapter 5). Important to note is that meticulous surgical hemostasis, even if it prolongs total operation time, results in reduction of peri-operative blood loss and in consequence in better outcome.

2. **The piggyback technique is the preferred technique of graft implantation.**

   Both techniques provides similar patient and graft survival (Chapter 4). Also morbidity, retransplantation rate and post-operative liver and kidney function is not different between the two techniques. However, the piggyback technique provides shorter anhepatic phase, revascularization time and warm ischemia time, which may be responsible for a quicker recovery of liver function. Moreover, blood loss is significantly reduced, when piggyback technique is used. Also the costs of the procedure are lower, as the VVB is not necessary in the piggyback technique. In view of these facts the piggyback technique should be preferred whenever possible.
3. The end-to-side caval anastomosis is a simple and safe procedure in the piggyback liver transplantation, allowing a very wide anastomosis without major risks of venous outflow obstruction.

End-to-side caval anastomosis can be performed without routine use of a temporary portocaval shunt and with minimal intraoperative blood product requirements (Chapter 5). It can be also safely used in first and second retransplantations. This technique of outflow reconstruction is recommended when piggyback the technique is used.

4. There is no difference in the outcome in different reperfusion protocols in terms of survival, graft function and morbidity, especially ischemic type biliary lesions.

However, the sequence of graft reperfusion may be particularly relevant in compromised liver grafts, such as livers from non-heart-beating donors, older or steatotic donors, small-for-size grafts in living donor liver transplantation as well as in recipients with poor cardiopulmonary reserve. This subject has not received much attention so far and thus more research in this area is warranted (Chapter 6).

5. Loss of technical variant grafts from deceased donors in children with body weight less or equal to 10 kg can be prevented by adequate size matching of donor and recipient. It appears that a D/R weight ratio below 4.0 is relevant for a successful outcome.

If D/R body weight ratio raises grafts tend to be large for size and complications may arise leading to graft loss. In deceased donors it is not possible to determine partial graft weight at the time of acceptance of the donor for particular child. That can only be determined after reducing or splitting the whole liver. This is in contrast to the situation in living donors, where beforehand graft weight and volume can be determined on basis of CT scans or MRI. Therefore, in deceased donor situation donor/recipient weight ratio can be very useful in matching of donor and recipient and preventing graft loss, especially in children with low body weight.