Studies on predictability of early graft function after liver transplantation
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Publication date:
2005

Link to publication in University of Groningen/UMCG research database

Citation for published version (APA):
chapter 8

Summary, conclusions and future perspectives
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Summary

Liver transplantation has changed the future of patients with end-stage liver disease. Nowadays one year patient survival reaches 90% in experienced centers. Most patients die in the early phase after transplantation. After this initial period patient survival approximates survival curves of the healthy population. This thesis focuses on early graft function after orthotopic liver transplantation and the factors determining such function. Chapter 1 provides an introduction to liver transplantation and provides an overview of factors implicated in early postoperative liver graft function. At the end of chapter I the aims and outline of the thesis are presented. In chapter 2, a retrospective study of 125 liver transplantations in adult patients is presented. It contains an analysis identifying risk factors for primary dysfunction including initial poor function and primary non-function. Donor, recipient and surgical parameters were evaluated for their predictive capacity for primary dysfunction. Since there is no consensus on the criteria of dysfunction we used two criteria sets known from the literature. No risk factors for postoperative dysfunction could be identified for either of the two definition sets. However the criteria set of Ploeg et al., using ASAT and prothrombin time, determined from day 2 through 7, showed that patients with a primary dysfunction had significantly higher morbidity and mortality, compared to patients with a well functioning graft.

We conclude that initial poor function after liver transplantation remains unpredictable, irrespective of the way it is defined. Taking this into account we did not search further in this field of demographic and disease characteristics. The next two chapters explored whether test performed in the liver after explantation from the donor and before actual implantation in the recipient could predict postoperative transplant function. The MEGX-test, performed in vivo in the donor to measure the metabolic rate of lidocaine conversion to MEGX, has been proposed as a function test for donor livers to predict post-operative organ function. In the study presented in chapter 3, we investigated whether the MEGX formation rate measured in needle biopsy specimens in vitro correlates with the rate of MEGX formation in vivo. The in vivo MEGX test was performed in the donors and in the recipients on day 1 and 2. The in vivo and in vitro MEGX tests were compared with post transplant liver function in the recipients in order to investigate their possible relevance as a predictor for graft function.
The MEGX formation rate in needle biopsy specimens in vitro showed a significant correlation with the MEGX serum concentration found in the donor. A low rate of MEGX formation in the biopsy specimens tended to predict initial poor function of the grafts. In the donor, the MEGX test did not correlate with general liver function after transplantation. Only the MEGX serum concentration in the recipients on day 2 gave an indication of graft function. MEGX formation in liver biopsy specimens in vitro properly reflects metabolic function of that particular liver. Therefore, liver biopsies may be a valuable tool to help predict liver function in vivo. However, the MEGX test alone is not sufficient to provide a gold standard to predict liver function in livers destined for transplantation. Due to the limited information that can be gained by the MEGX test in biopsies alone we explored other function tests in liver slices. In liver slices the original structure of the liver is retained. Such an integrated in vitro system may be a better tool to study metabolic capacity of a donor liver. For this study, described in chapter 4 surgical waste material remaining after reduced size or split liver transplantation in children was used to prepare slices and isolated hepatocytes. The viability of these preparations as well as drug transport and metabolism functions were determined and related to graft function in 32 liver recipients. The in vitro tests used in this study apparently did not select non-viable livers. In vitro preparations of the primary non-function grafts occurred in the investigated group showed normal viability, metabolic and uptake function. The results indicate that either the presently used viability tests are not sensitive enough to detect potential organ failure or that other factors than the hepatocyte viability at the time of transplantation are of predominant importance for the graft function of the recipient. In this respect the role and viability of non-parenchymal cells need further elucidation. Also the interrelationship or interdependency of the different liver functions hampers quantitative and qualitative assessment of liver function. Additionally graft function is not only determined by the condition of the donor or graft, but also by the condition of the recipient. Therefore, in chapter 5 we investigated the value of determining the gastric mucosal pH measurements as a measure of splanchnic perfusion. This test has been proposed as the ideal monitor of aerobic metabolism in intestinal mucosa, which is sensitive to alterations in splanchnic perfusion. A low pH has been shown to be a predictor of poor outcome in cardiac and aortic surgery and claims in the field of liver transplantation have
been published as well. Forty patients were included. Gastric mucosal pH and gastric mucosal pH, corrected for systemic pH, were compared with regard to initial liver function and morbidity. Eighty percent of the patients had at least one episode with a gastric mucosal pH < 7.32, and 84% of these had a concomitant arterial pH lower than 7.32. No differences in morbidity were found between patients with a gastric mucosal pH < 7.32 and those with a gastric mucosal pH > 7.32. If gastric mucosal pH was corrected for arterial pH, only 49% of the patients had an episode during transplantation with a corrected gastric mucosal pH < 7.32. Comparing these patients with the group that did not have such a low pH episode we found that flow in the venovenous bypass system was significantly lower (2.9 versus 3.4 L/min., p < 0.02) in the first group. Also ALAT and ASAT were higher and antithrombin III levels and lidocaine clearance rates were lower and protrombin times were longer in the group with corrected gastric mucosal pH < 7.32. However, no differences with regard to major morbidity and mortality were noted. It is concluded that gastric mucosal pH during liver transplantation should be corrected for arterial pH. Patients with a corrected gastric mucosal pH < 7.32 are more likely to develop initial liver function tests disturbances, but morbidity is not different from patients with gastric mucosal pH > 7.32. Therefore this test has limited value in the setting of liver transplantation.

In chapters 6 and 7 we studied whether endotoxin and cytokine levels might predict postoperative graft function. Both donor, recipient and surgical factors can be held responsible for increased levels of endotoxin and cytokines. Such increased levels can therefore be regarded as the ultimate common denominator of negative influences on the graft with possible repercussions on its performance. In chapter 6 we tried to identify the source and plasma levels of endotoxin, tumor necrosis factor alpha and interleukin-1 and interleukin-6. In a prospective study endotoxemia could only be demonstrated in 20% of 40 consecutive patients. In 75% of patients with endotoxemia, endotoxin appeared during the anhepatic phase and quickly resolved after reperfusion. Endotoxemia was not related to any clinical adverse event.

Only levels of tumor necrosis factor determined in the recipient before transplantation were found to be predictive of postoperative complications. Tumor necrosis factor was released from the graft after reperfusion and initial levels after reperfusion were related to predonation levels in the donor. We conclude that monitoring endotoxin, tumor necrosis factor alpha and
interleukin-1 and interleukin-6 is of a very limited value in predicting outcome. Chapter 7 presents the results of a prospective randomized placebo controlled study where patients were randomized in a group with and a group without selective decontamination of the digestive tract (SDD). We investigated whether perioperative endotoxemia during liver transplantation could be prevented with SDD and whether endotoxemia had any relation with a compromised graft function and the occurrence of infections. Thirty-one patients undergoing elective orthotopic liver transplantation received either SDD (n=15) or placebo (n=16), which was started at least 7 days before transplantation. Endotoxin levels were measured in blood perioperatively. Patients were scored daily for signs of liver dysfunction and infection. SDD did not prevent endotoxemia. Endotoxemia was neither associated with initial poor function nor with any routine liver function test. Infections were more prominent in patients without endotoxemia. Therefore endotoxemia could not be shown to affect postoperative graft function or the incidence of postoperative infections. Neither can SDD prevent perioperative endotoxemia. Translocation of endotoxin may not be relevant in liver transplantation.

Conclusions

It appears from these studies that early graft function cannot be reliably predicted on the basis of donor, recipient and surgery related demographic or biochemical variables analyzed in the context of the studies presented in this thesis. The MEGX-test performed either in vivo or in vitro in biopsies or liver slices of the donor liver also failed to predict early graft function. A test reflecting splanchnic perfusion in the recipient and thereby characterizing the recipient’s condition was again not able to predict clinically significant graft function disturbances of the graft. Finally, the presence or absence of endotoxemia and the levels of tumor necrosis factor-alpha, interleukin-1 and interleukin-6 showed no relation with graft performance or outcome. Endotoxemia could not be prevented by selective decontamination of the bowel. For the time being graft function remains an enigma. The current practice of refusing donor livers on the basis of clinical or biochemical parameters should therefore be considered questionable.
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Future perspectives

Early graft dysfunction after liver transplantation deserves ongoing attention. Early graft dysfunction increases post transplant morbidity and mortality and leads to an increased need for retransplantation. This latter fact results in an increased demand on the already restricted donor pool. Consequently graft dysfunction leads to an increase of the costs of liver transplantation.

The first item will be to define a proper criteria set of early graft dysfunction. So far, there is still a lack of such a definition validated in a large transplant population.

Until now, the occurrence of dysfunction after solid organ transplantation is a given fact. Several ways are open to solve the problem. First further studies are needed to discover the mechanisms of organ dysfunction after transplantation. In this respect the observation that organs from living donors perform better on the short and long term after transplantation compared to organs from brain death donors needs attention. Studies analyzing the influence of brain death on organ performance might provide insight into the mechanisms of organ dysfunction. Also more basic approaches on the molecular or genetic level might shed more light on the origins of organ dysfunction. The effects of the agonal phase of the donor, organ harvesting and preservation on gene expression in the hepatocytes needs further elucidation in order to analyze their influence on cellular performance. Such basic and mechanistic approaches will probably not provide immediate answers. Therefore, there is ample room for more practical approaches. Organ performance after transplantation might be improved by conditioning of the donor before retrieval of the organs. It has been shown that optimizing glucose metabolism in intensive care patients, for example regulating glucose levels between certain limits improves outcome in these patients. It seems logical to explore this also in organ donors, especially since glucose regulation influences energy (glycogen) content in the graft. Glycogen is the source for ATP and ATP content of the donor liver has proven to be of importance for post transplant organ function.

The function of the donor liver can also be improved by application of the concept of ischemic pre-conditioning as introduced by Clavien. This concept is applied
during liver resection. Post resection liver damage as expressed by serum ASAT and ALAT levels are lower when before the transection of the parenchyma the liver is made ischemic by a short period of clamping of the vessels followed by a period of reperfusion. This concept is also applicable in donors before explantation of the graft.

Another and practical approach is the introduction of machine preservation. Although not universally accepted machine preservation of kidneys is performed in several centers in the world and reports of viability testing are published. Due to its dual circulation machine preservation of livers is more complex. However, if available harvested livers of dubious quality can be assessed for their viability. Several laboratories are currently exploring this possibility and designing or testing such devices. It is even conceivable that quality of such machine preserved damaged organs can be improved by interventional metabolic strategies.

As one of the pioneers of liver transplantation has already stated in the past the recipient can offer a hostile environment to a liver graft and cause dysfunction. Therefore it is conceivable that measures to prevent such a hostile environment can prevent dysfunction of a transplanted liver. Such measures can be taken in several ways. We can try to improve the condition of the patient by a regimen of nutrition. Indirectly, this might improve postoperative graft function if specific additions like glycine or essential fatty acid free diet are made.

A more aggressive approach of infusing glucose, glucagon, insulin and amino acids might also improve liver function. Optimizing the nutritional status might not only directly influence post operative organ function, it might also prevent infections and prevent metabolic derangements. So, there is a need for trials in humans that improve the nutritional status of the recipient. Optimizing the recipient might not only include the nutritional status but also normalize inflammatory response and liver function.

An other practical approach might be Bio Artificial Livers (BAL’s) or artificial liver support. In a BAL, hepatocytes either of porcine or human origin are maintained in a bioreactor. Through which the patients blood or plasma is directed. Such a device replaces liver function and this may be helpful in case of malfunctioning grafts as has been reported in the literature. Liver support devices work in a different way. They remove toxins through a combination of hemodialysis, hemofiltration or absorption by charcoal or albumin. They treat...
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the effects of a malfunction graft; the production of toxins. Also reports are available of the use of liver assist devices in case of liver dysfunction after transplantation.\textsuperscript{24,25}

Finally the current situation in the field of liver transplantation is that organ dysfunction and especially early dysfunction cannot be predicted. It happens but we do not now when and how severe. Due to its implications in terms of morbidity, mortality and possible need for retransplantation with its subsequent use of additional livers and the incremental costs of the procedure it remains an important subject for research. Research should first be directed towards efforts to understand the basic mechanism of the problem and related interventional strategies. Up till that moment other measures to treat the consequences and sequellae of the dysfunction should be investigated, tested and used.
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