Organ donation for transplantation

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Chapter 11

SUMMARY, CONCLUSION AND RECOMMENDATIONS.

The central theme of this thesis was the continuing organ shortage. Several factors have been held responsible for this shortage, including refusal of permission for organ donation by the next-of-kin, insufficient recognition of potential organ donors by the medical staff, and -unjustified- discard of donors by transplant teams either due to logistic reasons or because of medical reasons. Apart from the logistic reasons, we have explored these different causes for organ shortage. With respect to the problem of medical discard we have focused on the liver, because transplantation of a viable liver graft is an important prerequisite for patient survival due to the lack of extracorporeal liver support. In this chapter we will summarize and discuss the findings of the studies in the previous chapters. Finally, recommendations for the future are given.

In chapter 2, the problem of refusal of permission by the next-of-kin was addressed. Interviewing people confronted with the request for organ donation in the (recent) past, allowed to get insight in their feelings and motivations to decide as they did. The study showed that the question for organ donation to the family always comes unexpectedly, since their hopes are aimed at the survival of their beloved. The anticipation of organ donation appeared to stand very much at right-angles to their feelings. This made the question very delicate. Another problem encountered was that the family should decide on a problem of which they cannot oversee the consequences. Such a situation can easily lead to (communication) problems. Some recommendations to 'smoothen' the donation request were given: Families should be addressed in a clear and empathic way avoiding unrealistic hopes. This not only demands professional and social skills from the requester, but the family should also be given time to come to terms with the bad news.

Chapter 3 concentrated on the problem of recognition of potential organ donors by the medical and nursing staff. This problem has gained a lot of interest lately, and it is considered as one of the most important factors hampering further progression of organ transplantation. In our study (only) 2 braindead donors were missed in a period of 4 years. This underscores that lack of recognition of potential (braindead) donors may not be as important as suggested in other studies. However, improvement appears to be possible in recognizing non-heart beating donors, since 13 of such potential donors were missed in the 4 years studied. The study had a few drawbacks, however. It concentrated on

trauma victims only, and it was performed in a large trauma center annex transplantation center with a transplant coordinator in the vicinity. Thus, thresholds to call the transplant coordinator were low. The study is probably only representative for large regional hospitals in The Netherlands, but it does not reveal the situation in smaller hospitals with limited trauma facilities and no interface with transplantation medicine. Preferably, the study should be repeated in a prospective way in a large number of hospitals of different sizes and with different specialities available.

Efforts to decrease the organ shortage should not only be directed at reducing the number of refusals by the next-of-kin and improving support from hospitals and hospital personnel, but also at defining appropriate organ-specific selection criteria for organs. Validated selection criteria might prevent the unjust discard of suitable organs but also prevent the transplantation of non-functioning organs. In the next chapters, our focus shifted towards selection criteria for liver donors. In our introductory chapter we mentioned that almost one in three livers offered were not selected for transplantation because of medical reasons. Chapter 4 gave an overview of the factors involved in the selection process of a donor liver at the moment a donor was offered. We made clear that selection of a suitable liver is a complicated process. Many donor factors should be taken into account: bacterial and viral status, age, length of hospitalization, hypotension, steathosis, laboratory data. In fact, in the chapter a plea for a holistic approach of the donor is provided: the donor should be seen as a whole. Viral and bacterial status play a role as important as the age of the donor or laboratory tests. However, few of the factors mentioned are absolute contra-indications for liver donation. The condition of the recipient needs to be considered too: the doctor has to weigh whether a further postponement is still possible or whether transplantation should no longer be delayed.
Chapter 5 compared the donor criteria from a group of failed grafts with those of a group of successful grafts. Remarkably, a significant difference was found between groups for the length of time the donor stayed in hospital before explantation: donors of livers that did not function after grafting, were hospitalized for a longer period of time than donors of a successful graft. From a methodological point of view it may be argued that the design of the study was not appropriate: comparing a single center successful group with a multi-center group of failed liver grafts. Ideally, a multi-center study with a matched pairs design should have been performed. However, within the practical constraints of the study the method is acceptable. Moreover, our findings converge with findings published by other groups (for references see chapter 4).
In chapter 6, we used regression analyses to see which donor parameters influenced final transplant outcome. Results indicated that in the time Eurocollins was used as preservation solution, the pH of the donor has been of importance.

However, this effect disappeared after the introduction of UW-solution as preservation solution. Length of hospital stay of the donor also differed significantly between successful and less successful grafts too, similar to the results in chapter 5. However, this parameter did not significantly effect final transplant outcome in the regression analysis. No other donor parameters with a significant effect on transplant outcome were identified.
The impact of the introduction of UW-solution on clinical liver transplantation was also studied in chapter 7. This chapter dealt with early postperfusion liver damage and liver function. The introduction of UW solution caused significantly less cell damage and equal immediate postoperative function, despite significantly longer preservation times. These results indicate that the prolonged preservation time made possible by UW does not have a detrimental effect on liver function after transplantation.
The results of chapters 6 and 7 indicate profound changes in the quality of liver preservation with the introduction of UW solution. Both studies prove the superiority of UW-solution over Eurocollins for liver preservation. Because of the longer preservation made possible with UW-solution, liver transplantation changed from an emergency procedure into a semi-elective operation. The introduction of UW-solution appears to have had effects on donor selection as well. The results of both studies imply that in (retrospective) studies analyzing the relation between donor parameters and transplant outcome it is necessary to make a distinction between EC-preserved and UW-preserved livers; analyzing EC- and UW-preserved livers together in one group would mean the introduction of a bias. In addition, the findings may indicate that, because of the new improved preservation solution, the condition of the liver has become less important. This result would have a possible impact on selection criteria for liver donors, i.e., less stringent criteria.
In chapter 8, the search for relevant donor parameters was 'fine-tuned'. In order to exclude the influence of the quality of the preservation and of the condition of the recipient on transplant outcome, a matching procedure was introduced. Again, the results showed that currently applied selection criteria do not play a major role in predicting final transplant outcome as reflected in graft survival. More postoperative complications and a longer stay in the intensive care were encountered in case a less ideal donor liver was used. However, the differences did not reach statistical significance.
From the chapters 5, 6, and 8 we may conclude that in our study populations traditional selection parameters played a very limited part in the ultimate result of liver transplantation.

Since clinical donor parameters did not predict transplant outcome, we studied whether functional tests on isolated hepatocytes may have clinical value. This approach was made possible because of the longer preservation times allowed

by UW-solution. In chapter 9, hepatocytes were isolated from large biopsies or - in case of partial transplantation- from the not-transplanted liver part. Hepatocytes could be isolated successfully from livers obtained from young children as well as from donors up to 64 years old, although the yield varied greatly. The duration of liver preservation in UW did not significantly influence cell yield, viability and cellular ATP. The rate constants of taurocholic acid transport, Trypan blue exclusion during uptake experiments, morphological integrity and ATP content were used for comparison of the quality of the hepatocytes isolated from accepted or from discarded livers. No significant differences in the above mentioned quality parameters were observed between hepatocytes isolated from the different (sub)groups. The lack of differences in cell quality between groups of accepted and discarded livers may imply that the measured parameters were not sensitive enough to predict liver quality. On the other hand, it may also lead to the conclusion that again unjust discard of potentially viable livers has occurred. Confirmation of that hypothesis will need a group of liver transplants showing a bad liver function after transplantation. Fortunately, such livers were not present in the series.
In chapter 10 attempts were made to isolate the hepatocytes from (small) needle biopsies, since these biopsies will be practically possible if it ever would come to an introduction into clinical practice. Whereas isolation from large pieces of liver tissue was quite successful, isolation mostly failed in case of needle biopsies. The main reason for this lack of success is as yet an enigma, which in itself hampers a further introduction at this stage.

Conclusion

The question for organ donation is a delicate one. A grieving and uncertain family is approached at a time their hopes are aimed at the survival of their beloved. Special skills are required to present the question to the next-of-kin under these circumstances.
In large hospitals with trauma facilities and a transplant coordinator in the vicinity, doctors and nurses adequately recognize potential -brain-dead- organ donors. However, considerable improvement is possible in the recognition of 'non-heart-beating' donors.
There is little ground for a strict selection of liver donors on the basis of traditionally applied clinical parameters. Such a policy will unnecessarily limit the donor pool, while applying less restrictive criteria may not cause less graft survival. Laboratory data should be used on indication only, not on a screening basis. That is, if the anamnesis gives reason to believe that diseases or trauma of the liver exist, specific liver function tests should be requested.
Unfortunately, our study provided no new criteria to replace or supplement the old ones. In this respect, it should be realized that the liver is a very complex organ. To look for the ultimate liver test that will make all other tests superflu-

ous is like the search for the 'philosopher's stone' that was thought to be able to turn lead into gold. Most likely, a combination of tests will provide an answer which liver can be transplanted and which not.

Recommendations

In chapter 2 we gave some recommendations how to improve the donation request. Here we would like to add a few comments. First, it should be pointed out that the 'opting-out' system[1] for organ donation can avoid the problems encountered in our study to a large extend: the family is not confronted with a decision *they* have to make, but with a decision already made by the deceased. Although that decision may be as hard for them to be confronted with, it probably can save them the uncertainty of whether or not they made the correct decision. In case the 'opting-in' system is chosen in a country, it is necessary to train doctors and nurses, in order to overcome their diffidence and to avoid displeasure in the donor's family. In this respect, the Eurotransplant initiative Eurotransplant Donor Hospital Education Program (EDHEP), or similar initiatives, should be supported strongly. In this program nurses and specialists (on a voluntary basis) receive a training in breaking bad news, in how the donation request should fit in this process, and in how to provide aftercare to the relatives. Preferably, such initiatives should be an obligatory part of the training of future doctors and specialists.

The results in chapter 3 open the possibility that past donor estimates are too optimistic nowadays. In 1984, Jonkman and Ploeg estimated a potential of 700 donors annually for The Netherlands [7]. However, in the last 5 years, the number of donors reported to the Dutch Transplant Coordinators was rather stable at about 350 donors a year. A possible explanation for the difference may be that since the publication of Jonkman and Ploeg, a gradual decline of the number of traffic accidents in The Netherlands has occurred: in 1982, 1710 traffic accident deaths were registered. In 1992, this number had fallen to 1285 (Centraal Bureau voor de Statistiek, personal communication). In comparison, in Belgium in the same year, death toll of modern traffic was 1671. Thus, part of the discrepancy between countries like the Netherlands and Belgium in the number of organs harvested (e.g., donor kidneys: *NL:* 29.7/million population; *B:* 35.1/million population) should probably be attributed to this difference in

[1] *'Opting-out' refers to a donation system in which it is assumed that the individual consents to remove his/her organs after death, unless explicitly stated otherwise. As a result the relatives do not have to decide about a donation request. In Europe, the system applies in e.g. Austria and Belgium. The opposite is the 'opting-in' system, in which -most times- the relatives of the deceased give consent to remove the organs,* ***at the time of death****. In this situation the next-of-kin must make a decision in line with the supposed will of the deceased. This system is used in most of the European countries.*

lethal traumata in both countries. This discrepancy cannot be attributed to the difference in the donation system alone. Consequently, presentation of statistics on organ yield per country, would be more readily explanative if they included the variation in the number of trauma deaths. For instance, expressing the number of available kidneys as number/million population/thousand traffic accidents yields a number of 23.1 for the Netherlands and 21.0 for Belgium.

The clinical studies on the effects of donor parameters on transplant outcome in this thesis, showed that relations between donor quality and transplant outcome are difficult to find in a clinical setting. The main problem is that a controlled experimental design is not possible. The 'ideal' study design would be to transplant all livers offered and just look at the results. From an ethical point of view this approach is questionable. Consequently, in clinical studies, several pitfalls may have their effects on the results.
First, allocation bias should be avoided. So far, studies published are performed on transplanted livers. Consequently, a rather homogeneous study population is studied. It is not investigated if the livers discarded on the basis of the used criteria indeed would not have functioned. Because of the ethical limitations, within the context of clinical studies there is no clear way to approach the problem of allocation bias. The only possibility left to a center is to register post-transplant function of livers discarded by them but accepted by another center. Another solution to avoid allocation bias is to perform animal experiments. Only these types of experiments allow an controlled experimental design to study the influence of different factors in the donor on liver transplant outcome.
Second, the introduction of UW has changed liver transplantation profoundly. EC- and UW-preserved grafts are not comparable, and should in the future be analyzed seperately. Finally, the condition of the recipients varies greatly. Since this condition also influences final transplant outcome, a source of bias is present and should also be corrected for in future studies. Matching may provide such a solution.

A search for other criteria, that can be used in clinical practice, should be started, because traditional selection parameters were not indicative for liver viability. The criteria to be looked for should be an indication of liver viability: the ability to restore normal function and overcoming the damage resulting from harvesting and preservation [5]. For the liver this may be more complicated than other organs because of the complex tasks the liver has to perform in maintaining body homeostasis.
To us the frontier that separates life and death is a very definite one. However, on a cellular and subcellular level there is not a distinct caesura, but a gradual decay of enzyme systems. This decline of cellular function will inevitably lead to

a less favourable starting position of the liver. The question is where and when the point of no return is reached. Research should aim at getting insight in the factors that determine that point of no return. In the past, this kind of research has concentrated on preservation of the organ. However, it may be wise to extend this research to the donor. For example, nutritional status of a liver appears to be very important as Boudjema et al. have found in the rabbit and the pig [2]. Livers of fasted animals were more 'PNF-prone' as livers from fed animals. This should be attributed to a depletion of liver glycogen stores. Via a breakdown to glucose, subsequently to pyruvate via the Embden-Meyerhof glycolytic pathway, and finally a further breakdown in the Krebs-cycle, glycogen is an important source for the generation of ATP. Depletion of glycogen therefore deprives the liver of ATP in the initial posttransplant period. Other important mechanisms to concentrate on are membrane integrity (which in itself depends on the presence of high energy phosphates), Ca^{++}-homeostasis, and the effect of acidosis. A possible role of radicals (oxygen free radicals, nitric oxide) should also be considered. Finally, in case of the liver, one should take the exocrine function of the liver, i.e. the excretion of bile, into account.

New technologies may provide important information here. First, magnetic resonance spectroscopy (MRS). The technique is based on the responses of protons in a strong magnetic field to the effect of a brief radiofrequency pulse. To explain all details of the technique is beyond the scope of this thesis. It suffices to say that this originally chemical technique allows the assessment of concentrations of metabolites in vivo. In the past years, several studies have been published using MRS as a tool to assess the amount of different metabolites in an organ to be transplanted, especially ATP, NADP, etc [3,4,6,8,11]. First results look promising, but it has to be realized that progress is slow because of the relatively low resolution, and of the relative insensitivity of the system [9]. Positron emission tomography (PET) may be another -and complementary- tool. This technique allows to quantitate metabolic processes in vivo. Although there are physical limitations to the resolution also (but currently far better than in MRS), the technique is very sensitive. The technique is based on the introduction of positron-emitting isotopes into substances that participate in normal metabolism. So, PET visualizes the dynamics of metabolism. For instance, temporary ischemia causes a decrease in RNA and protein synthesis. However, when blood flow is reestablished before the point of no return is reached, there is full recovery of these processes [1]. With PET, the protein synthesis can be visualized and -with the appropriate mathemetical model available- also be quantified, using ^{11}C-labelled amino acids. Therefore, the effects of different donor parameters or the effects of different preservation effects on protein synthesis can be studied, while PET's non-invasive character also permits the assessment of final transplant outcome, i.e. survival of the graft. Similarly, ^{11}C-thymidine can be used to assess regeneration capacity of the liver [10].

Since PET is rather laborious, MRS may be more feasible in the clinical situation. MRS may provide an extra point of decision whether or not to transplant the organ. PET in its turn has a unique possibility to study the dynamics of liver metabolism in animal experiments. The technique allows to study the regeneration of liver function in time in the same animal. Finally, the technique may be worthwile in 'resuscitation' studies, i.e. studies in which it is tried to improve the condition of the donor liver before it is actually transplanted.

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