Optimising outcomes after liver transplantation

Valorisation

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This chapter will discuss how the research results presented in this thesis could be used in clinical practice. The implications of the study results to the wider community will be described. Lastly, the necessary steps to implement machine perfusion into clinical practice will be reviewed.

Implications of research results for the wider community

In Australia, there has been a steady increase in the number donor livers deemed unsuitable for transplantation over the last ten years. Despite the strong wishes of donor families to use the organs of their loved ones to save the lives of others, the number of liver declined for transplantation increased from 26% in 2005 to 43% of in 2014. On the other hand, annually about 10% of patients with end stage liver disease waiting to undergo life-saving liver transplantation became ineligible as their disease progressed beyond acceptance criteria for transplantation. The decreasing rate of liver utilisation is not only a pressing problem in Australia, but has been reported around the globe. In the United Kingdom, the proportion of livers used for transplantation has dropped by 16% between 2005-06 and 2014-15.[1,2] Furthermore, Orman *et al*. found that in the US, liver non-use increased from 15% in 2004 to 21% in 2010,[3] which was accompanied by declining annual liver transplant rates.

If we could make better use of the organs currently available, it would mean that the wishes of more donor families could be honoured. Furthermore, as this could be achieved without an increase in the number of organ donors, it would be the most cost effective way to save the lives of patients that succumb to their disease while waiting to undergo liver transplantation.

Currently a large proportion of livers declined for transplantation are from organ donors who donate their organ after the cessation of circulation (donation after cardiac death, DCD). The use of these liver grafts is currently limited by the slightly increased risk of primary non-function, especially when transplanted into a high-risk recipient. More importantly, the development of ischaemic type biliary strictures (ITBS) in up to one in three recipients limits long-term graft survival.[4,5] As a results, the cost per life year gained is far greater in DCD donors where € 112,376 was spent per annum compared to € 88,913 per year for those that receive a liver donated after brain death.[6]

The aim of this thesis was to characterise the sequence of events associated with the development of ITBS, as this is currently the most limiting factor in the utilisation of DCD livers. Improved knowledge about the pathophysiology of ITBS may help find new therapies or preventing measures, and these may benefit the wider community. In

context, the use of normothermic machine perfusion was explored as a tool to assess graft function of livers currently declined for transplantation Combined, these two avenues of research have an impact on the wider community as a whole as liver disease and organ donation touches the lives of many patients worldwide.

The implementation of normothermic machine perfusion

The application of normothermic machine perfusion (NMP) has several advantages over the use of conventional simple cold storage. First of all, the quality of marginal donor organs can be preserved which would allow for the use of more livers currently declined for transplantation.[7] Furthermore, it possibly allows for extended periods of preservation, which in turn facilitates long distant transport but also improves transplant logistics as the transplant can take place during daytime hours.[8] In addition, results from several animal studies have indicated that NMP is preventing biliary injury, which could reduce the incidence of ITBS.[9,10] Equally importantly, graft function can be assessed during perfusion at 37°C, which could avoid transplanting a non-viable graft.

An NMP protocol was established at the Princess Alexandra Hospital and ten livers declined for transplantation were successfully perfused. Based on the viability criteria previously described by other centres,[7,11,12] seven could potentially have been used for transplantation. Over the last 2 years, 146 DCD liver grafts were declined for transplantation in Australia. If 70% of these grafts could have been recovered using NMP, this would have increased the donor pool by 16%. A similar prediction of the effect of NMP on organ donor numbers was made by Mergental *et al.*.[13] Based on the number of livers declined for transplantation and the results of their pilot study, they estimated that a 15% increase in the total number of donor livers could be achieved in the United Kingdom.

Based on the experience with NMP described in this thesis and reports of other centres that have implemented the technique in clinical practice, the next aim is to start using those livers that are deemed viable during NMP for transplantation.

What is required to implement NMP in clinical practice?

Machine perfusion post static cold storage or in transit

Currently, NMP has been applied following a period of cold storage as well as during transit.[8,12] Although in transit perfusion limits the period of cold preservation injury to about one hour, it comes with some logistical challenges. It would mean that a new

vehicle fitted with a main power supply needs to be purchased to facilitate the transport of this large piece of equipment. However air-transportation is often required in countries such as the United States, Canada and Australia and the use of NMP in a small airplane has not previously been performed. Furthermore, banked matched blood will have to be taken to the donor hospital to serve as perfusate during NMP although the blood may not be used if a DCD donor does not die within the currently accepted time frame. Lastly, in some instances the airplane is shared between the abdominal and cardiothoracic team when retrieving organs from donors outside the metropolitan area. As the maximum cold ischaemic time of a heart is already in jeopardy when flight time exceeds 2 hours, there may be time restrictions in establishing NMP for the donor liver prior to transportation.
Therefore in Australia, NMP will probably only be initiated at the recipient hospital following a period of conventional cold storage.

Organ donor inclusion criteria

An important consideration is which liver grafts require NMP prior to transplantation. Some reported studies have included “within criteria” grafts in their perfusion studies (8). These livers are however already acceptable for transplantation using current empirical criteria and the application of NMP exposes them to the potentially catastrophic effects of pump failure. Furthermore it will not increase the number of grafts available for transplantation but it may increase the costs associated with using them. In fact, as the appropriate criteria to determine viability are still being established, perfusion of “standard criteria” donor livers could potentially lead to a reduction in the number of transplants. One group of patients that could benefit from machine perfusion of “standard criteria” grafts are those with a high model for end-stage liver disease (MELD) in the intensive care. Machine perfusion reduces the reperfusion injury and this could reduce the incidence of post-reperfusion syndrome during transplantation.[14]
However as increasing the number of donor livers available for transplantation is the primary goal, livers currently declined for transplantation should be the target of NMP. Furthermore, the use of livers with evidence of structural damage or organ donors infected with hepatitis B, C or HIV should be avoided. Initially, warm ischaemic time of DCD donors will be limited to 30 minutes, which can be extended once we become more experienced.

Criteria for viability assessment

A standardised protocol will be established outlining the criteria used to determine viability. Based on the pre-clinical results described in this thesis, lactate clearance below 2 mmol/L within two hours will be the main component. Furthermore, the liver

needs to have a satisfactory macroscopic appearance and both the surgeons as well as the anaesthetist involved in the care of the recipient need to agree on proceeding. While the recipient is prepared for transplantation, machine perfusion will continue until transplantation. This period is anticipated to be up to six hours.

Recipient selection

The selection of suitable recipients of these high-risk NMP livers is crucial in obtaining favourable long-term outcomes. In countries such as Australia and the United Kingdom, no nationwide liver transplant waiting list exists and organ allocation is performed by individual transplant centres. Patients with hepatocellular carcinoma could be suitable low-risk recipients to receive an NMP perfused liver. These patients often do not have end stage liver disease with portal hypertension and ascites, which makes the transplant operation more straightforward from a technical perspective.

Commercial machine versus custom-made setup

Currently, two commercial machines have been used for normothermic liver perfusion in clinical studies in Europe and the United Kingdom however both are not approved by the Therapeutic Goods Administration for use in Australia.[8,15] These machines cost up to AUD 260,000, which excludes the disposables (personal communication). These are priced between AUD 9000 and AUD 18,000 per perfusion. The perfusion setup described in this thesis, is comprised of components used for ECMO, and costs AUD 1500 per perfusion.
As experience was gained with our custom made setup and it is significantly cheaper than the commercially available machines, we will continue to use the perfusion machine described in this thesis.

Cost implications for transplant program

An increase in donor numbers will come at a price. Not only is machine perfusion more expensive than conventional static cold storage, staff and facility costs needed to run them have to be considered. Currently, the kidneys from DCD donors are often the only abdominal organs retrieved from DCD donors and their retrieval is performed by an urologist or general surgeon. If the livers of those donors are considered for transplantation, this will mean that HPB surgeons will have to perform more retrievals and an increase in surgical staff will need to be considered. Despite the increase in cost in the short term, it will reduce the cost required for ongoing care of patients with end stage liver disease. Furthermore, if the incidence of biliary complications can be limited by the use of NMP, it will significantly reduce the costs of ongoing care for liver transplant recipients.

In conclusion, machine perfusion will have a distinct impact on global transplantation practices in the near future as it will ultimately lead to a significant increase in the number of livers available for transplantation.

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