Cold Ischaemia Time and Living Donor Kidney Transplantation

Subjects: Transplantation

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The best therapy for patients with end-stage renal disease (ESRD) is kidney transplantation. Results underline the need to keep cold ischaemia time (CIT) as short as possible in living donor kidney transplantation (LDKT) (ideally < 4 h), as a shorter CIT in LDKT is associated with a statistically significant lower incidence of DGF and higher graft survival compared to a prolonged CIT. However, clinical impact seems limited, and therefore, in LDKT programmes in which the CIT might be prolonged, such as kidney exchange programmes, the benefits outweigh the risks. To minimize these risks, it is worth considering including CIT in kidney allocation algorithms and in general take precautions to protect high risk donor/recipient combinations.

kidney transplantation living donors

1. Introduction

Not only does kidney transplantation reduce the risk of morbidity and mortality and is associated with a better quality of life, but it also has superior outcomes compared to other forms of renal replacement therapy ^{[1][2][3]}. Unfortunately, kidney transplantation is not readily available for all end-stage renal disease (ESRD) patients in need due to donor organ shortage; although the waiting list for patients with ESRD is decreasing and the number of transplantations is increasing, only around 46% of patients on the waiting list received a donor kidney in 2019–2020 in the United Kingdom. Furthermore, during this period, 285 ESRD patients (4%) did not survive whilst on the waiting list ^[4]. To counter this problem, several therapies and strategies have been implemented to improve the availability of kidney grafts and the number of transplantations.

Over the years, living donor kidney transplantation (LDKT) has proved superior to deceased donor kidney transplantation (DDKT) ^{[5][6][7]}, especially as it facilitates pre-emptive transplantation ^[8]. One of the other many benefits of LDKT is that the cold ischaemia time (CIT) is shorter since generally donor and recipient operations happen in the same centre and on the same day. Transplant professionals feel that this is important since a shorter CIT leads to what is believed to be a better outcome in the recipient ^{[9][10][11]}. This principle is based on the outcomes of CIT in the deceased donor kidney transplantation literature; it is known that a short CIT is associated with better transplant outcomes ^{[9][10]}, and prolonged CIT is strongly correlated with a higher incidence of delayed graft function (DGF) ^{[12][13][14][15]} and a possible impact of CIT leading to a higher incidence of graft failure and graft loss ^{[12][16][17][18][19]}.

To expand the options of having LDKT for patients with incompatible donors, kidney exchange programmes were introduced. The first national Kidney Exchange Programme (KEP) in Europe was the Crossover Kidney Transplantation Programme started in 2003 in the Netherlands ^{[20][21]}. It uses an algorithm to provide live donor kidneys to people with ESRD that cannot receive a kidney from their potential donor because of AB0 incompatibility or donor-specific antibodies. In April 2007, the United Kingdom initiated the UK Living Kidney Sharing Scheme (UKLKSS) to match incompatible recipients to an appropriate kidney donor ^[22]. In this system, the donor kidney might be transported from one centre to another, which is associated with longer anticipated CIT, in contrast to kidney exchange programmes in the Netherlands and Canada, where the donor travels to the recipient centre where both live donor nephrectomy and transplant operations take place with CIT comparable to direct LDKT.

2. The Impact of CIT on Graft Function and Graft Survival in LDKT

The discussion about CIT and its potential influence on graft and patient outcomes of LDKT is topical in a decade where ideas about nationwide, and on a small scale even international, LDKT exchange programmes are becoming more ambitious than ever before ^{[23][24]}. In the UK, for example, LDKT from the UKLKSS account for 14% of all LDKT ^[25]. With kidneys from living donors travelling from donor to recipient centres across and between countries, long distances are being bridged, CIT will inevitably increase. In deceased donor kidney transplantation, prolonged CIT is proven to be associated with worse transplant outcomes, higher incidence of DGF and a higher incidence of graft failure and graft loss ^{[9][10][12][13][14][15][16][17][18][19]}.

The literature thus far has always stated that CIT is not a clinically relevant issue in LDKT and that living donor kidneys can tolerate even prolonged CIT of >16 h when shipped between states in the USA for example ^[26]. Besides an increased importance of kidney paired exchange programmes with longer CIT compared to direct LDKT, living donor kidneys include more expanded criteria donors which may impact graft outcomes ^[27]. These expanded criteria donor kidneys might be more sensitive to prolonged CIT compared to standard criteria living donor kidneys.

LDKT recipients in kidney paired exchange programmes implicitly are higher risk recipients compared to recipients in non-kidney paired exchange LDKT; the KEP group consists of more highly sensitized patients, higher donor and recipient age, more human leucocyte antigen (HLA) antibodies, more retransplantations, longer waiting time before transplantation, and therefore a longer period of dialysis and less pre-emptive transplantation ^[25]. This theoretically would result in a higher risk of complications, impacting graft and patient survival. However, no difference was found in graft survival between KEP and non-KEP, only a significant difference in DGF.

The results show an adverse effect of a CIT longer than four hours on the risk of DGF and a decrease in the 1- and 5-year graft survival of kidney grafts after LDKT significantly, favouring a CIT of less than four hours. To put those outcomes into perspective: the numbers needed to treat would be 50 for DGF and 35 for 5-year graft survival. A marginal impact of CIT on graft survival and graft quality has been demonstrated and hoped that these findings will contribute to the expansion of KEPs and provide evidence to support international collaboration in KEPs. People

should keep in mind that patients or transplant professionals should not be discouraged to accept a kidney with prolonged CIT, and results should not lead to fewer transplant opportunities for patients. As shown above ^[25], results of LDKT outperform deceased donor kidneys even with prolonged CIT. However, these outcomes still might be optimized since a higher incidence of DGF leads to a longer hospital stay which may result in less quality of life for the patient and increased costs per kidney transplant such as in DDKT ^{[28][29]}.

Multiple strategies could be implemented to shorten the CIT in LDKT; the most effective would be simultaneous live donor nephrectomy and LDKT in case of direct donation. In this case, there is hardly any clinically relevant CIT. However, many centres cannot organize this, given the need for two theatres which are not utilized at maximum efficiency to enable simultaneous donor and recipient surgery, and this is the reason most centres default to consecutive living donor nephrectomy and LDKT. In case of kidney paired exchange, there are other differences besides simultaneous versus consecutive surgery. In many kidney exchange programmes or kidney sharing schemes, the kidney travels from the donor centre to the recipient centre (as described in ^[25]), which obviously leads to increased CIT compared to LDKT not transplanted via a kidney sharing scheme. A strategy to keep the CIT to a minimum would be for the donor nephrectomy to be carried out in the same centre as the transplant, as practiced in the Netherlands and Canada, amongst others. In case of LDKT, this is relatively easy to facilitate, since live donors are healthy people who are perfectly capable of travelling (if willingly), with the downside that distances may be long, and it may be difficult for family to travel along and provide support. In addition, for kidney sharing scheme programmes in case of donor organs travelling to recipient centres, the CIT could be incorporated as a variable in the matching algorithm. If this is not an option and the kidney has to be transported over a long distance, one could investigate the use of donor organ machine perfusion. It is shown that hypothermic machine perfusion (HMP) reduces the risk of DGF and 1-year graft survival in deceased donor kidney transplantation [30][31], but evidence amongst LDKT is minimal and the only study performed did not detect any difference in DGF [32]. Future studies should explore the idea to deploy HMP during shipping of the kidneys with an expected prolonged CIT of more than four hours. Together, with existing literature on LDKT risk factors [11][26][25][32], it could be deemed cost-effective to support kidneys from high-risk donor-recipient pairs with HMP or deploy HMP during shipping of the kidney when a prolonged CIT of more than four hours is expected $\frac{[33]}{[33]}$.

3. Conclusions

The results, based on 164,179 patients, underline the need to keep CIT as short as possible in LDKT (ideally < 4 h), as a shorter CIT in LDKT is associated with a statistically significant lower incidence of DGF and higher graft survival compared to a prolonged CIT (>4 h). However, clinical impact seems limited, and therefore, in LDKT programmes in which the CIT might be prolonged, such as kidney exchange programmes, the benefits outweigh the risks ^[25]. To minimize these risks, it is worth considering including CIT in kidney allocation algorithms to reduce DGF, graft failure, and in general take precautions to protect high risk donor–recipient combinations.

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