ORIGINAL ARTICLE

Outcomes of kidney paired donation transplants in relation to shipping and cold ischaemia time

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SUMMARY

To assess the impact of shipping distance and cold ischaemia time (CIT) of shipped organs in a kidney paired donation (KPD) programme, we evaluated the outcomes of the initial 100 kidney transplants performed in the Australian KPD programme. In a 44-month period, 12 centres were involved in fifteen 2-way, twenty 3-way, one 4-way and one 6-way exchanges. Sixteen kidneys were transplanted at the same hospital (CIT 2.6 ± 0.6 h) and 84 required transport to the recipient hospital (CIT 6.8 ± 2.8 h). A spontaneous fall in serum creatinine by at least 10% within 24 h was observed in 85% of recipients, with no difference between nonshipped and shipped kidneys. There were two cases of transient delayed graft function requiring dialysis and patient and graft survival at 1 year were 99% and 97%, respectively. There was no difference in recipients of nonshipped compared with shipped kidneys with regard to serum creatinine at 1 month (mean difference (MD) 7.3 μmol/l, 95% CI −20.2 to 34.8, $P = 0.59$), 1-year graft survival (MD 3.9%, 95% CI −5.4 to 13.2, $P = 0.41$) or patient survival (MD −2.4%, 95% CI −10.0 to 5.2, $P = 0.54$). Despite prolonged CIT for interstate exchanges, the programme's decision to ship donor kidneys rather than the donor appears to be safe.

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Key words
cold ischaemia time, delayed graft function, kidney paired donation, living-donor kidney transplantation, organ transport

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Introduction

Delayed graft function (DGF) is known to influence short and long-term graft outcomes. DGF is the consequence of well-described risk factors, including donor creatinine, donation after cardiac death and cold ischaemia time (CIT), the latter being one of the main predictors of DGF [1]. Living-donor kidney transplantation (LDKT) is associated with superior long-term recipient and graft survivals compared with deceased kidney donors [2], because of avoidance of prolonged CIT and shorter dialysis waiting-time or avoidance of dialysis [3]. Unfortunately, in up to 50% of the otherwise appropriate potential live donor/recipient pairs, ABO blood group incompatibility or human leucocyte antigen (HLA) sensitisation between donor and recipient is a major barrier to live donor kidney transplantation [4]. One strategy to overcome HLA and ABO incompatibilities is through kidney paired donation (KPD). In KPD, recipient and their willing, but incompatible live donor

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agree to exchange kidneys with another incompatible pair so that both recipients receive compatible organs from strangers [5,6].

Generally, pairs matched in a KPD chain are from different transplanting centres, which may be several hundreds of kilometres apart. In some KPD programmes, including The Netherlands and Canada, a living donor in KPD travels to their matched recipient's hospital, so that the donor nephrectomy and kidney transplant are performed at the same institution in an effort to minimise CIT [7]. Counterarguments to donor travel and favouring shipping live donor kidneys include the donor unfamiliarity with transplant team, the risk of loss of donor anonymity and disrupted family care and support [6]. Furthermore, because the assessment and acceptance criteria for living donors vary between programmes, there is significant risk of declines of matched donors or delays in accepting a donor by the recipient's programme because of the need for additional testing. For these reasons, some KPD programmes have now embraced the practice of shipping live donor kidneys [7–9]. This practice is relatively new and there are only a handful of reports describing the incidence of DGF and outcomes [8–10]. The Australian KPD programme has adopted the practice of shipping live donor kidneys in adherence with three key criteria: first, the anaesthetic induction time (AIT) for each live donor surgery must occur simultaneously for all donors within the same chain; second, the organs are transported using commercial airlines; and third, CIT should be <12 h. Compliance with these requirements and with some exchanges occurring between three time-zones and up to 3700 km apart could result in some organs being transplanted with unacceptably long CIT and subsequent DGF. Thus, the purpose of this study was to compare shipped to nonshipped living-donor kidney transplants performed in recipients participating in KPD through the Australian Kidney paired eXchange (AKX) programme with respect to adherence to simultaneous AIT, differences in DGF as well as early and 1-year graft and patient outcomes.

Materials and methods

Study design

This study was a longitudinal cohort analysis of the first 100 living-donor kidney transplants conducted through the AKX programme between October 2010 and May 2014. Basic donor and recipient demographics, operating times, including AIT, shipping distance, total CIT, warm ischaemia time (defined as the time between kidney off ice to reperfusion) and other factors known to affect early graft function and failure such as side of donor nephrectomy and number of arteries [11,12], were retrieved from the AKX registry. Graft outcomes, including initial function, creatinine at 1 month, graft survival and DGF were retrieved from the ANZDATA registry. DGF was defined as the requirement for dialysis within seven days post-transplantation. Outcomes in recipients of AKX kidneys, including early graft function, prevalence of DGF, patient and graft survival were compared to outcomes in the cohort of recipients of directed live donor kidney transplants from the 2010–2013 period in the ANZDATA registry.

Procurement and transport of kidneys

All the logistical aspects related to organ procurement and transport were organised by the AKX programme coordinator (C.W.). The donor and recipient surgeons communicated before the nephrectomy to review donor anatomy, agree on cold-storage solution and coordinate operating theatre times. Donor nephrectomies were performed at the donor institution according to their preferred surgical approach. The AKX programme coordinator was responsible to ensure simultaneous donor AIT on the day of chain exchange surgeries. No significant operative or postoperative complications occurred. Once the organ was removed from the donor, it was immediately flushed with cold-storage solution. The organs were packaged and labelled using specific AKX live donor kidney procurement procedures and transported in a single-use, cold-storage container using established protocols. All organs shipped interstate were transported using commercial airlines. Perfusion machines were not used for any of those shipped organs and are currently not been considered for the transport of live donor kidneys. The AKX programme coordinator verified flight plans and backup flights. The donor kidneys were transported to and from the airport utilising couriers with detailed tracking documentation. There was no requirement for simultaneous recipient surgery start time within the same chain and recipient surgery commenced shortly after the kidney was delivered at the recipient's hospital. CIT was calculated from the exact time the organ was cross-clamped and the exact time of reperfusion of the organ, adjusting for time-zone difference as appropriate.

Statistical analysis

Statistical analysis was performed with STATA 13.1 (StataCorp. 2013. STATA statistical software. College Station,

TX: StataCorp LP.) Fisher's exact test was employed for categorical data. Wilcoxon's signed-rank test was used for paired continuous data. All *P*-values are 2-sided and a *P*-value ≤ 0.05 was considered to be statistically significant.

Results

Basic demographic data of participating recipients and donors are summarised in Table 1. In a 44-month period, 17 donor surgeons were involved in fifteen 2-way, twenty 3-way, one 4-way and one 6-way exchanges. The donor kidneys originated from 12 different centres in six cities across Australia, four centres were in Sydney, three centres in Melbourne, two centres in Perth, one each in Adelaide, Brisbane and Newcastle. No donor withdrew consent on day of surgery. There were no swap failures because of a failure in transport and none of the pairs refused the exchange due to the proposed transport. There was no significant difference in recipients of shipped versus nonshipped kidneys with regard to gender distribution, age, cPRA, donor–recipient age difference and proportion of patients allocated an ABO-incompatible matched donor. Donor age tended to be higher in non-shipped (57 ± 8 years) compared with shipped kidneys (52 ± 10 years, $P < 0.07$). Mean (±SD) within chain AIT variability was 8 ± 18 min (range 0–105) and 85% of AIT were within 15 min (69% <5 min). Due to unforeseen circumstances, the AIT differed by 15–30 min from the scheduled time in 10% of cases. A pre-arranged delay in AIT of >30 min was agreed in five cases. Donor kidneys were 87% left-sided and 18% had >1 artery to anastomose. In all these cases, dual arteries were anticipated, either because the donor had two arteries or a single artery with early branching close to the aorta on the computer tomographic imaging of the donor. All right-sided kidneys had a single renal artery. Sixteen (16) donor kidneys were transplanted in a recipient at the same hospital (CIT 2.6 ± 0.6 h) and 84 kidneys were shipped to another transplanting hospital (CIT 6.8 ± 2.8 h, $P < 0.001$), either within the same state or interstate (Tables 1 and 2). Shipping distance between centres within the same city or state was <150 km; between interstate centres along the east coast, it ranged 655–1600 km; and between centres from the east to west coast, it ranged 2140–3620 km. No kidneys were lost in transport. Road transport within the same city or state was used in 37 cases and the mean CIT for these kidney transplants was 4.0 ± 1.1 h. Interstate air transport with a mean shipping distance of 1810 ± 1125 km was required for 48 kidneys; in these instances, the east–east coast CIT 6.8 ± 1.1 h ($n = 28$) and the east–west CIT was 10.5 ± 1.7 h ($n = 20$) (Fig. 1). Of the latter group, four kidneys were transplanted with a CIT of >12 h, the maximum CIT was 13.8 h, and all four kidneys had immediate function with a fall in serum creatinine of >10% within the first 24 h. For the kidneys requiring shipping by air, deviation from the pre-arranged transport plan was required in 19 cases. In two cases, delays during donor surgery resulted in increased CIT by 1 h; in 17 cases, the organ was shipped with an earlier flight with an average reduction in CIT of 1.4 ± 1.0 h shorter than the anticipated CIT.

Table 1. Recipient and donor data for Australian Kidney paired eXchange transplants. Results are reported as mean ± SD or number (and percentage).

	Recipients		Donors	
	Nonshipped	Shipped	Nonshipped	Shipped
N	16	84	16	84
Female gender (%)	12 (75)	48 (57)	7 (44)	35 (42)
Age (years)	52 ± 11	47 ± 14	57 ± 8	52 ± 10
Donor age – recipient age (years)	0.5 ± 12	5 ± 16		
ABO-incompatible matched donor (%)	2 (13)	16 (19)		
cPRA (%)	71 ± 35	54 ± 38		
cPRA range				
0–50%	5 (31)	37 (44)		
50–75%	2 (13)	9 (11)		
75–95%	5 (31)	23 (27)		
95–100%	4 (25)	15 (18)		
Graft number				
1st	12 (75)	63 (75)		
2nd or more	4 (25)	21 (25)		

Table 2. Outcomes of live donor kidney transplants in recipients of kidney paired donation (KPD) transplants versus directed live donor transplants in Australia and New Zealand 2010–2013. Results are reported as mean ± SD (and 95% confidence interval) or number (and percentage).

	KPD recipients		Directed live donor kidney transplants
	Non-shipped	Shipped	
N	16	84	1270
Cold ischaemia time (h)	2.6 ± 0.6	6.8 ± 2.9	3.2 ± 2.3
0–4 h	16	12	
4–8 h	–	46	
8–12 h	–	22	
12–14 h	–	4	
Revascularisation time (min)	33 ± 12	38 ± 16	
Immediate function	14 (88%)	71 (85%)	1131 (89%)
Delayed graft function (%)	0	2 (2.4%)	47 (3.7%)
Serum creatinine at 1 month (μmol/l)	105 ± 26	112 ± 50	123 ± 86
Mean difference (95% CI)		7.3* (20.2–34.8)	
1-year patient survival (95% CI)	100%	98% (96.5–99.5)	99% (98.5–99.5)
Mean difference (95% CI)		−2.4* (−10.0 to 5.2)	
1-year graft survival (95% CI)	94% (89–99)	98% (96.5–99.5)	97% (96.5–97.5)
Mean difference (95% CI)		3.9* (−5.4 to 13.2)	

*P = NS.

Short- and medium-term outcomes were excellent. Immediate graft function with a fall in serum creatinine was observed in 86 cases (Fig. 2), with no difference between shipped and nonshipped kidneys. There were two cases of delayed graft function requiring dialysis, and in both cases, CIT was <7 h (4.4 and 6.7 h, respectively) (Table 2, Fig. 2); in both cases, allograft function recovered and serum creatinine at 1 month were 133 and 171 μmol/l, respectively. There was no significant difference in serum creatinine at 1 month according to shipping distance (Fig. 3). Serum creatinine at 1 month in recipients of nonshipped (105 ± 7 μmol/l) compared with shipped kidneys (112 ± 6 μmol/l) did not differ significantly (mean difference 7.3 μmol/l, 95% CI −20.2 to 34.8, P = 0.59). The 1-year patient and graft survival were 98% and 97%, respectively; there was 1 case of early graft loss due to surgical issues in a recipient of a nonshipped kidney (CIT 2.4 h). Graft and patient survival did not differ in recipients of nonshipped compared with shipped kidneys (mean difference graft survival 3.9%, 95% CI −5.4 to 13.2, P = 0.41, patient survival −2.4%, 95% CI −10.0 to 5.2, P = 0.54). In comparison, during the period 2010–2013, the 1-year patient and graft survival of 1270 living-donor grafts in Australia and New Zealand were 99% and 97%, respectively (Table 2). In this cohort, DGF was reported to be 3.7%.

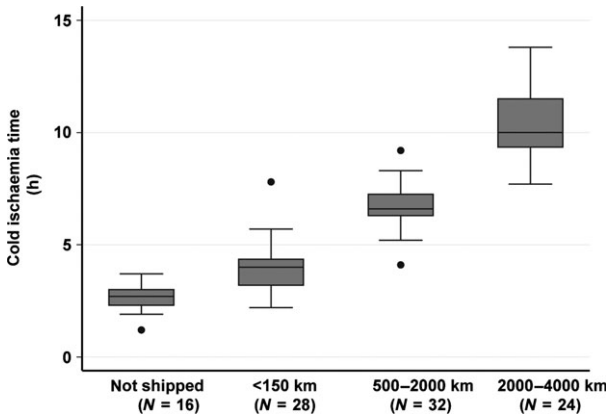

Figure 1 Cold ischaemia time in relation to shipping distance.

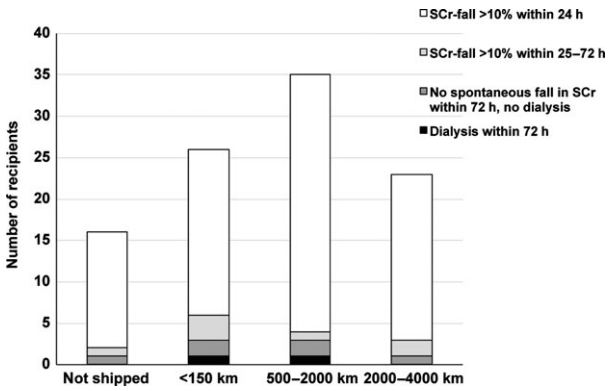

Figure 2 Initial function of Australian Kidney paired eXchange kidneys by shipping distance.

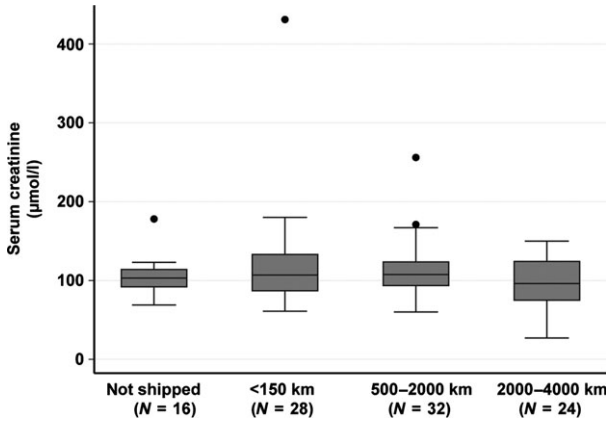

Figure 3 Serum creatinine at 1 month in recipients of Australian Kidney paired eXchange kidneys in relation to shipping distance.

Discussion

The analysis of the Australian cohort of paired exchange kidney transplants demonstrates that despite a mean CIT of 6.8 h, shipped live donor kidneys have short-term outcomes and 1-year graft survival rates similar to when kidneys are procured in the same institution as the recipient in directed live donor kidney transplantation. Furthermore, the 2.4% rate of DGF among our shipped cohort is below the reported national rate for all living-donor transplants of 3.7% reported in the ANZDATA cohort.

Kidney paired donation has undergone considerable refinement since the concept of exchanging kidneys between incompatible pairs was first proposed [13] and the first KPD transplants reported [14]. Many KPD programmes are now multicentre national or regional programmes [7] and participating facilities can be several thousand kilometres apart. With KPD, procurement of the donor kidney can occur at the same institution as the recipient procedure or at a different institution, in which case the procured kidney must then be shipped from the donor hospital to the recipient hospital. When the kidney is procured at a facility distant to the recipient, the donor kidney is subject to increased CIT. This problem is obviously of importance for vast countries such as Australia, Canada or the United States and to lesser extent for smaller size countries in Europe. Only a few reports describe the incidence of DGF and outcomes in relation to prolonged CIT in live donor kidney transplantation [8–10]. Simpkins *et al.* [10] identified 393 cases of LDKT in the UNOS database that had 6–8 h of CIT due to unintended delays. The 10-year graft survival of these live donor kidney recipients with extended CIT was equivalent to the remainder of the group. In a multicentre review, shipped live donor kidneys with a median CIT of 7.2 h and a mean transported distance of 1270 km demonstrated no DGF, as defined by a need for dialysis in the first week [8]. More recently, Treat *et al.* analysed the shipped kidney cohort of recipients participating in KPD through the National Kidney Registry (NKR). The mean shipping distance was 2630 km (range 200–4520) with mean CIT of 12.1 ± 2.8 h. There was no difference in the incidence of DGF (shipped versus nonshipped cohort 1.8% vs. 0%, respectively) or 1-year allograft survival (98% in both cohorts) [9].

In our cohort, the mean shipping distance for 48 kidney-flown interstate was 2810 ± 1125 km with mean CIT of 8.4 ± 2.3 h. Despite the increase in CIT in recipients of KPD kidneys, outcomes of KPD kidneys were comparable to conventional LDKT and the 1-year graft survival was 97% vs. 97%, $P = 0.97$. Interestingly, no case of DGF requiring dialysis was seen in recipients of an organ with CIT >10 h associated with longer shipping distances and the only two cases of DGF were seen with CIT <7 h, suggesting some factor intrinsic to either the organ procurement or shipping process other than prolonged CIT was responsible. In one of these cases, a pre-implantation biopsy showed severe acute tubular necrosis. There was no difference in initial function or mean serum creatinine values at 1 month between the shipped and nonshipped groups suggesting that prolonged CIT of up to 14 h has minimal impact on kidney allograft and outcome. Laparoscopic live donor nephrectomy has the disadvantage of increased warm ischaemia time, which could be factor contributing to DGF [15], and could be associated with a higher incidence of early graft failure when right kidneys are used [12]. However, in our cohort, warm ischaemia time did not differ in recipients of shipped versus nonshipped kidneys and although there was a tendency, albeit statistically insignificant, for right kidneys to be shipped rather than being used locally, this technical challenge was not associated with increased risk of DGF. There was also no effect of ABO-incompatible donor matching [16] and early graft function or DGF.

Shipping kidneys is a complex undertaking that requires cooperation between the programme coordinator, multiple transplant physicians, surgeons, operating rooms, transplant nurses and couriers. Our study shows that organ transport using commercial airliners can be successfully arranged despite the requirements to adhere to simultaneous donor surgeries and minimisation of CIT. When simultaneous donor surgeries for a KPD chain are performed, real-time communication between

involved operating rooms and the AKX programme coordinator is established to ensure that all donors have simultaneous anaesthetic induction time. It is interesting to observe that a significant deviation of >15 min difference in donor AIT within the same chain can still occur in up to 10% of cases due to unforeseen circumstances during induction of anaesthesia. Nevertheless, this variability does not significantly affect the shipping schedule. In two cases (4% of kidneys shipped by air), a delay in donor surgery resulted in a 1 h increase in CIT, while in 17 (35%) cases the kidney was able to be shipped on an earlier flight resulting in a reduction in projected CIT.

The limitations of our study are the relatively small number of organs with substantially extended CIT, as only 12 organs were reperfused with a CIT of over 10 h and only four of these had a CIT of 12–14 h. Moreover, the short duration of follow-up precluded identifying the effect subtle differences in CIT could make over time. Debout *et al.* [17] analysed graft and patients survival at 1, 5 and 10 years in recipient of heart-beating deceased donors in relation to CIT. They estimated that for each additional hour of CIT, the risk of graft failure was multiplied by 1.013 [17]. Thus, it would be prudent to remain cautious and attempt to maintain CIT as short as possible when shipping live donor kidneys. On the other hand, the slightly increased risk of long-term graft loss in relation to ischaemia time must be balanced against the risk of increased graft failure if patients were to wait on dialysis for an organ with lesser anticipated CIT, as it has been shown that kidney transplants performed after more than 2 years of maintenance dialysis have a 39% worst projected 10-year graft survival [3].

Kidney paired donation programmes have facilitated live donor kidney transplantation in many patients who would have otherwise been unable to undergo transplantation due immunologic incompatibility. Our initial experience using mostly shipped kidneys demonstrates good short-term graft survival. Our data also demonstrate that, while logistically challenging, it is feasible to adhere to simultaneous start time of donor surgery while maintaining CIT as short as possible. Any KPD programme involved in long-distance shipping of living-donor kidneys should carefully monitor CIT and graft outcomes to validate and confirm these findings.

Authorship

RA, PF: participated in research design. RA, HP, PAC and PF: participated in the writing of the paper. RA, HP, CW and PF: participated in the performance of the research. RA, PAC, CW and PF: participated in data analysis.

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Conflicts of interest

The authors have declared no conflicts of interest.

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