Comparison of first and second kidney transplants from the same deceased donor

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Abstract

Background. Cold ischaemic time (CIT) may negatively influence graft function, increase the risk of acute rejection, and have adverse effects on graft and patient survival. This holds true especially for expanded criteria donors. As multi-centre studies on the impact of CIT are potentially biased, we performed a retrospective single-centre analysis of both kidneys from the same deceased donor transplanted consecutively into two recipients.

Methods. A retrospective analysis of 80 kidneys from 40 donors transplanted into 80 recipients between January 1989 and December 2007 was conducted. Transplantations were performed successively due to logistic reasons resulting in a longer CIT for the second transplantation. We compared the outcome of the first (Rank 1) vs. the second (Rank 2) transplantation of the same donor. Ten donors/20 kidneys were allocated in the Eurotransplant Senior Program (ESP).

Results. Overall, no significant difference was found for the number of rejections, delayed graft function (DGF), functional data (creatinine, creatinine clearance and GFR) or graft survival despite a significant difference in CIT of Rank 1 recipients (8.3 h) vs. Rank 2 recipients (14.3 h). Subgroup analysis of kidneys transplanted in the Eurotransplant Senior Program (CIT Rank 1: 7 h vs. Rank 2: 12 h) also showed no difference for all the items studied. Donor kidneys ≥65 years transplanted at Rank 2 had a higher rate of DGF when compared with kidneys from donors <65 years transplanted at Rank 1, and function was better for the young Rank 1 recipients for all the time points measured. Graft- and patient survival did not differ.

Conclusions. We found no difference between the successively transplanted kidneys of the same donor, not even for the expanded criteria donor organs. Nevertheless, assuming a ‘safe’ CIT is not justified, and CIT should always be kept as short as possible.

Keywords: cold ischaemic time; expanded donor criteria; ischaemic time; paired kidney; renal transplantation

Introduction

Kidney transplants (KTX) are often not handled as highly urgent procedures but postponed due to logistical reasons, operating theatre time schedules and the necessity of pre-transplant dialysis in some recipients. Cold ischaemic time (CIT)—the time between influx of preservation solution into the donor and removal from the ice storage for anastomosis in the recipient—has been identified as an independent risk factor for delayed graft function (DGF) (need for dialysis in the first week following KTX) [1–4] and acute rejection [5,6]. DGF may increase acute rejections [5,7] and have adverse effects on graft and patient survival [5,7,8]. Furthermore, DGF was found to prolong hospital stay and thus to increase costs [9]. Kidneys from aged donors were found to be even more susceptible to the negative impact of long cold ischaemic time [8,10]. The Eurotransplant Senior Program (ESP), which started in January 1999 and in which kidneys from deceased donors aged ≥65 years are transplanted into recipients ≥65 years, therefore aims at keeping transport time short. Allocation in the ESP is preferably local taking into account blood group compatibility and waiting time, while ignoring HLA match.

As multi-centre studies are potentially biased because immunosuppressive strategies, surgical skills, and peri- and post-operative management may differ, we performed a retrospective single-centre analysis of both kidneys from the same deceased donor transplanted successively into two recipients in our department to determine the impact of CIT on graft outcome.

Material and methods

Between January 1989 and December 2007, 80 kidneys from 40 donors were transplanted into 80 recipients using an extraperitoneal approach. Donor kidney pairs were allocated to our centre due to a full-house HLA match (3 donors—6 recipients), acute hepatitis B/C (7 donors) and donor age ≥65 years (15 donors). Of these, 10 donors/20 kidneys
Table 1. Demographic, immunologic, peri- and postoperative data

| Comparison |
|-----------------|-----------------|----------------|
| Rank 1 recipient | Rank 2 recipient | P     |
| Recipient age (median, years) | 53.6 years (4.6–71.9) | 58.3 years (2.9–71.9) | ns |
| Recipient gender | 15 female/25 male | 18 female/22 male | ns |
| Donor/recipient gender | ns | ns | ns |
| Same gender | 19 | 16 | ns |
| Different gender | 21 | 24 | ns |
| Female => male | 10 | 10 | ns |
| Male => female | 11 | 14 | ns |
| Donor age (median, years) | 51.0 (1.2–127.6) | 47.5 (7.4–117.3) | ns |
| Median waiting time (months) | 35 | 35 | ns |
| First transplantation | 5 | 5 | ns |
| Re-transplantation | 0 (0–36) | 0 (0–88) | ns |
| PRA mas./at transplant (median, %) | 34.7 | 33.5 | ns |
| Median follow-up (months) | 3 (0–6) | 3 (0–5) | ns |
| HLA-A,-B,-DR mismatches (median) | 8.3 (4.2–27.6) | 14.3 (5.3–34) | p<0.01 |
| Median cold ischemic time (h) | 48 min (13–180) | 49 min (21–95) | ns |
| Median anastomosis time (min) | 28% | 32% | ns |
| Overall rejections (%) | 23% | 28% | ns |
| First year rejections (%) | 16 | 21 | ns |
| DGF (patient number) | 58.5 (3–83) | ns |

were allocated to 20 recipients in the ESP. From among these donors, both kidneys were allocated to our centre on the basis of the Eurotransplant Kidney Allocation System (ETKAS), which takes into account waiting time, HLA match, distance to the explanting hospital (= expected cold ischaemic time) and other criteria [11].

For logistic reasons, most transplantations of both kidneys from the same donor were performed successively in our department, resulting in a shorter CIT for the first transplant (Rank 1) compared with the second transplanted kidney (Rank 2). The surgical technique was extraperitoneal with antirefluxive ureteral implantation and routine ureteral stenting. Immunosuppression consisted of a standardized triple therapy [calcineurin inhibitor, azathioprine (until 1995) or mycofenolate mofetil (from 1996 onwards), and corticosteroids] with dose reduction over time. Until 2004, only selected patients received induction therapy with an interleukin receptor antibody (graft loss in history due to immunological reasons, >4 mismatches). From 2004 onwards, all recipients received IL-2 receptor antibodies routinely. Rejections were treated by pulsed methylprednisolone bolus therapy, followed by conversion to tacrolimus and/or treatment with ATG in steroid-resistant cases. Data for the study were retrieved from our computer database, which stores all patient data, including follow-up visits, in an electronic patient record system. Loss to follow-up was defined as having no information on a patient for at least 12 months after the last visit (last information before August 2007).

To evaluate the impact of cold ischaemic time on graft function and outcome, we performed the following analyses:

(i) Rank 1 vs. Rank 2 recipients.
(ii) Rank 1 vs. Rank 2 of kidneys transplanted in the ESP.
(iii) Comparison of young donor kidneys transplanted at Rank 1 vs. kidneys from donors ≥65 years transplanted at Rank 2 as HLA mismatches and CIT did not differ significantly between these two groups.

For more comprehensive functional assessment of the transplanted kidneys, we not only evaluated creatinine levels but also compared creatinine clearance and glomerular filtration rate (GFR) calculated by urine collection and by the formulas of Cockcroft–Gault and Modification of Diet in Renal Disease (MDRD) on the basis of plasma creatinine, age, body weight, gender and ethnicity for the same time points. It is noteworthy that MDRD is supposed to be more accurate in renal impairment [12,13].

**Statistical analysis**

Statistical analysis was performed with the commercially available SPSS 14.0. Categorical parameters were compared by chi-square test, and continuous variables were assessed by the Mann–Whitney U-test. Graft and patient survival were calculated by Kaplan–Meier analysis, and tested for differences using the log-rank and Breslow test. A P-value <0.05 was considered significant.

**Results**

Of the 40 donors, 15 (30 kidneys) were aged ≥65 years. Immunological risk did not differ with respect to the number of re-transplantations or panel-reactive antibodies [historical (P=0.55); at time of transplantation (P=0.98)]. (For demographic, immunologic and perioperative data, see Table 1.) Rejection rate did not differ significantly. Recipients with DGF did not experience a higher rate of rejections (Rank 1: 31% vs. Rank 2: 42%; P=ns), but kidneys with DGF had a significantly worse graft survival (censored log-rank: 0.016; uncensored log-rank: 0.022). Eight recipients were lost to follow-up (Rank 1: 3; Rank 2: 5; P=ns).

Median creatinine (Figure 1) at 1, 3 and 12 months and annually for years 2–5 was 1.6 (0.6–9.7), 1.56 (0.67–4.67), 1.58 (0.54–5.53) and 1.63 (0.57–2.92), 1.63 (0.6–2.32), 1.75 (0.93–2.98) and 1.53 (0.85–2.65) mg/dL for Rank 1 recipients vs. 1.92 (0.69–6.05), 1.84 (0.7–5.89), 1.68 (0.69–3.51) and 1.85 (0.82–3.31), 1.60 (0.9–5.37), 1.99 (0.96–3.2) and 1.97 (0.95–5.13) mg/dL for Rank 2 recipients, respectively. Differences were not significant at any time point.

Median creatinine clearance (urine collection) for Rank 1 vs. Rank 2 recipients at 1, 3 and 12 months and annually for years 2–5 was 42 vs. 37 mL/min, 44 vs. 36 mL/min, 45 vs. 40 mL/min, 40 vs. 31 mL/min, 47 vs. 37 mL/min, 34 vs. 34 mL/min and 42 vs. 31 mL/min. Differences were not significant (see Figure 2). The same holds true for the GFR calculated according to Cockcroft–Gault (data not shown) and MDRD (Figure 2), which were not also significantly different.

Twelve grafts were lost: 7 due to chronic allograft nephropathy, 3 due to vascular problems, 1 with primary non-function and 1 for an unknown reason. Rank 1 vs.
Rank 2 KTX showed no difference in cumulative censored
graft survival (GS) (death with functioning graft=no loss)at 1, 3 and 5 years (91%, 84% and 84% for Rank 1/94%, 88% and 70% for Rank 2; log-rank: 0.98; Breslow: 0.671; P=ns) (Figure 3) or cumulative uncensored GS (death with functioning graft=graft loss) for the same time points (91.4%, 84% and 84% vs. 91%, 81% and 55%; log-rank: 0.16; Breslow: 0.559; P=ns).

One patient in Rank 1 who had lost graft function 1 month after KTX due to arterial problems died of infection 31 months after KTX. Of Rank 2, six recipients died 1–68 months (mean: 29.7 months) after KTX, three of infection, two of cardiac disease and one of liver cirrhosis. Except for one, all recipients in Rank 2 died with a functioning graft. Patient survival was significantly different in favour of Rank 1 recipients at 1, 3 and 5 years: 100%, 95% and 95% for Rank 1 and 93%, 88% and 72% for Rank 2 (log-rank: 0.02).

Subgroup analysis

Twenty kidneys from 10 donors were transplanted in the Eurotransplant Senior Program and had a significantly different CIT of Rank 1 vs. Rank 2 (Rank 1: 7 h vs. Rank 2: 12 h). Nevertheless, no difference was found for occurrence of rejections (3 vs. 5; P=ns) or transplanted kidneys with DGF (7 vs. 7). Kidney function [creatinine, creatinine clearance (urine collection), CG and MDRD] showed no difference between Rank 1 and Rank 2 recipients transplanted in the ESP at any point in time. As one graft of Rank 1 and two grafts of Rank 2 were lost, censored and uncensored graft survival did not differ significantly. The same holds true for recipient survival (two died in Rank 2 of pneumonia/sepsis; log-rank: 0.157).

Comparing donor kidneys aged ≥65 years transplanted at Rank 2 (n = 15) with kidneys from donors <65 years transplanted at Rank 1 (n = 27), we found—as expected—a significant difference for donor age (Rank 2 ESP: 66.7 years vs. Rank 1 <65: 43.6 years; P>0.01) and recipient age (70 vs. 49 years; P<0.01). As older donor kidneys were mostly allocated locally in the ESP, CIT did not differ significantly (12.1 vs. 12.5 h; P=ns) nor did HLA matches (4 vs. 3; P=ns). For the old donor kidneys, we found a higher rate of DGF (78% vs. 29%; P<0.05), but rejections were in the same range (33% vs. 22%; P=ns). Kidney function was better for the young Rank 1 recipients for all time points measured, but the difference did not always reach significance. Creatinine was significantly better for young Rank 1 recipients at Month 1 and 3 and Year 2, creatinine clearance (urine collection) at Month 1, 3 and Year 5. GFR according to CG and MDRD was significantly better at all time points except for MDRD–GFR at Year 2 and 3. Censored (log-rank: 0.684) and uncensored (log rank: 0.616) graft survival did not differ nor did recipient survival (log-rank: 0.73).

Discussion

For logistic reasons, two kidneys from the same donor are most likely transplanted successively if they are allocated to and transplanted in one centre. The longer CIT resulting for the second transplanted kidney potentially increases the risk of DGF and acute rejection. This may impact long-term graft function, especially of kidneys from aged donors, which are known to be more susceptible to non-immunologic damage during cold ischaemic time. So far, only six studies have compared the fate of both kidneys from the same deceased donor transplanted into two recipients. Only two of these studies evaluated the impact of CIT [14,15], while the other four studies focused on the impact of obesity [16], recipient body surface area [17], recipient age [18], or donor factors like age and gender [19]. Our study is the first to also evaluate recipients transplanted in the Eurotransplant Senior Program, in which kidneys from deceased donors aged ≥65 years are trans-
planted into recipients aged ≥65 years and the first to use meticulous assessment for comparison of renal function (CG and MDRD).

**CIT, DGF and rejection**

Even though cold ischaemic time was significantly shorter for Rank 1 recipients in our study, the rate of DGF did not differ. Similar results were reported by Giblin et al. [15], who found no difference in the DGF rate after a CIT of 19.9 vs. 25.6 h (3.8% vs. 7.3%). In contrast, in the study by Tandon et al. [14], the group with a shorter CIT (14.1 h vs. 19.2 h) had a significantly lower rate of DGF (16% vs. 39%). We found a 6–10-fold higher DGF rate compared to Giblin et al. [15] even though our CIT was five times shorter. One reason for this difference may be the very young donor age in the study of Giblin et al. (35.4 years). Median donor age was >20 years higher in our study, and old kidneys are known to be more susceptible to non-immunologic damage.

In our subgroup analysis of ESP recipients, we found no impact of the 5-h longer CIT on DGF, rejection or kidney function. A reason may be that CIT in the ESP is extremely short due to local allocation as suggested by the fact that the recipients transplanted at Rank 2 in our department still had a 2-h shorter CIT than the recipients transplanted at Rank 1 in the other comparative studies [14,15]. Nevertheless, the groups are too small to state this as a proven conclusion. That age by itself may be a risk factor for poorer outcome has been described. We also found a significantly higher rate of DGF in donors aged ≥65+ compared with younger donor kidneys even

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**Fig. 2.** Median creatinine clearance (millilitre per minute) according to MDRD (upper figure) and urine collection (lower figure) Rank 1 vs. Rank 2. Patients at risk for the respective time points are in the diagram. Differences were not significant.
though HLA mismatches and CIT did not differ significantly between the groups. Yet, as there are multiple other risk factors (e.g., final donor creatinine, arterial hypertension common in this group and atherosclerosis), this can only be hypothesised in the awareness of multiple confounders.

Results of other studies have shown that donor age >55 years and CIT are the strongest risk factors for DGF [2,4,20,21]. Especially kidneys from donors aged 65+ seem to be at a higher risk for DGF [8,10,22,23]. The impact of DGF on graft survival was found to differ, depending on when the studies were performed. Older studies did not detect a reduced GS after DGF [3,7], but more recent studies found that DGF can double the risk of graft loss [6], which is comparable to a full HLA mismatch situation [4,22,23]. These differences are most likely attributable to the increased number of expanded criteria donors [24]. The fact that there was no difference in DGF rates in our study may therefore explain why we did not find differences in graft survival, but results have to be weighed in the awareness of a small cohort size.

How long is a reasonable CIT? While data from the Collaborative Transplant Study (CTS) found no difference in graft survival rates for CIT of 7–12 vs. 13–24 h [25]. Offermann [26] showed that recipients with a CIT of 7–12 hours had a better graft survival than those with a CIT of 19 h and more. Many authors found that, especially, kidneys from donors aged 55 and older are more susceptible to the non-immunological damage occurring during CIT [1,2,4,23,27]. Even though the aim should be to keep CIT as short as possible in donors of all ages, but especially in aged donor kidneys, transplanting surgeons should keep in mind that nightshift transplantations were found to have more complications and a higher graft failure rate [28]. As our findings suggest that there may be a ‘safe’ cold ischaemic time of at least 12 h, in which even an aged kidney can be transplanted without negative effects, short CIT and daytime transplantation can almost always be achieved. Nevertheless, this conclusion is suggestive, and the studied group is too small to state this as a firm result. As a principle, CIT should always be kept as short as possible. If more than one kidney arrives in the same transplantation centre, all efforts must be taken to transplant in parallel and not successively.

Acute rejection (AR) rates did not differ significantly in our study, neither for the complete cohort nor for subgroups. This is in accordance with the findings of Tandon and Giblin [14,15]. The reason for our results may be that DGF, found to be a risk factor for AR by some authors [6,29], did not differ among the groups we studied.

Graft function

Overall, graft function did not differ between Rank 1 and Rank 2 recipients over a 5-year follow-up period irrespective of the method applied [creatinine, creatinine clearance (urine collection) Cockgroft–Gault and MDRD]. Amazingly, when comparing the graft function of aged kidneys transplanted in the ESP, no difference was found either, despite the supposedly higher susceptibility of aged donor kidneys and a 5-h longer CIT. As mentioned above, this may lead to the assumption that ESP donor kidneys seem to have a ‘safe’ time of cold storage and transportation of at least 12 hours. One has to take into account, though, the small sample size and the resulting limitations. The studies

![Cumulative censored graft survival](image)

**Fig. 3.** Cumulative censored graft survival (death with functioning graft=no graft loss) in months: Rank 1 (red, shorter CIT) and Rank 2 (green, longer CIT). Recipients at risk at the respective time points (insert at bottom of graph). Differences were not significant (log-rank 0.99; Breslow 0.671).
of Tandon [14] and Giblin [15] do not give functional data, and Giblin [15] only describes a more rapid change in creatinine for Rank 1 recipients. Cosio [19] found that donor age and gender as well as acute rejections have a negative impact on graft function, and Moreso [17] found a negative impact of recipient body surface on graft function at 1 year. Nevertheless, the latter two failed to compare Rank 1 with Rank 2 recipients.

Differences were mostly significant for graft function when we compared aged donor kidneys transplanted at Rank 2 with younger donor kidneys at Rank 1. This is an expected finding and underlines the better functional reserve known for younger kidneys.

Graft and recipient survival

The rank at which the transplantations were performed did not statistically affect censored or uncensored graft survival in our study, neither in the overall study nor in the subgroup analyses. It is noteworthy that, even though the differences in GS were not statistically significant, censored and uncensored GS were better for Rank 1 recipients after 5 years by 15% and 30%, respectively. Giblin [15] found a significantly better 5-year GS for Rank 1 recipients (72.2% vs. 64.9%). Different findings may be due to the high share of panel-reactive antibodies (PRA), which were found to be 16–18% in the comparative studies and different immunosuppressive protocols. Nevertheless, the statistical power of our relatively small group of 80 transplanted kidneys is low. Tandon [14] fails to give information on graft survival.

Patient survival was significantly higher for Rank 1 recipients than for Rank 2 recipients in our study, while it did not differ in the study of Giblin [15]. No data on patient survival were presented by Tandon et al. [14]. Reasons for different findings remain unclear and appear to be unrelated to the rank of transplantation, as the cause of death was not related to graft function, and rank of transplantation was not found to influence patient survival in the subgroup analysis, where even ESP recipients transplanted at Rank 2 had the same survival as young recipients transplanted at Rank 1.

Drawbacks of the study

One drawback of our study is the relatively small cohort size. A higher number of patients are needed to make firm conclusions. Also, in a time period of ~19 years, advances and adaptations of operational techniques, individual surgical skills of different surgeons, immunosuppressive therapy strategies, and changes in peri- and post-operative management may influence the outcome. Finally, the retrospective character of our study makes our results weaker than they would be in a prospective analysis.

Conclusions

This is the only study out of a total of seven investigating the impact of CIT on the fate of both kidneys from a deceased donor transplanted into two recipients at the same transplant centre. The authors conclude that

(i) Old donor kidneys are more susceptible to CIT than young donor kidneys.
(ii) Graft function, graft survival and DGF rate were not significantly affected by the rank of transplantation, but differences in favour of the shorter CIT were observed.
(iii) Maximum abbreviation of CIT is mandatory, even though the data of our study is suggestive of a ‘safe’ transportation and storage time. If logistically possible at the respective centre, both kidneys of the same donor should always be transplanted in parallel.

Conflict of interest statement.

None declared.

References

12. Hawley CM, Kearsley J, Campbell SB et al. Estimated donor glomerular filtration rate is the most important donor characteristic predicting graft function in recipients of kidneys from live donors. Transplant Int 2007; 20: 64–72
Lipoxygenase-derived hydroxyeicosatetraenoic acids—novel perioperative markers of early post-transplant allograft function?

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Abstract

Background. Active metabolites of arachidonic acid (AA), eicosanoids, strongly influence renal homeostasis. The aims of this study were to measure perioperative variations in lipoxygenase (LOX)-derived 5-, 12- and 15-hydroxyeicosatetraenoic (HETE) acids levels, and to examine whether (i) dynamics of these eicosanoid generation changes during the first 5 min of renal allograft reperfusion, (ii) examined HETE acids may influence perioperative 20-HETE generation, and (iii) LOX HETE may serve as perioperative markers of early post-transplant allograft function.

Methods. Sixty-nine kidney recipients were divided into early, slow and delayed graft function (EGF, SGF and DGF, respectively) groups. Blood was taken directly before, and in the consecutive minutes of graft reperfusion. HETE concentrations were measured using liquid chromatography. Creatinine levels were measured during the perioperative period, as well as during follow-up visits (first post-transplant year).

Results. Our results demonstrated significant differences in the concentrations and dynamics of HETE changes between the examined groups. Moreover, observed changes in HETE concentrations were strongly associated with post-transplant graft function and perioperative 20-HETE synthesis. Application of cut-off limits for newly introduced markers, that is 71.72 ng/mL for 5-HETE(5) and 12-HETE(12), resulted in 72.5% sensitivity and 81.5% specificity for SGF/DGF prediction. Moreover, mixed model analysis revealed that recipients classified according to results of 5-HETE(5) and 15-HETE(15) significantly differ in 1-year post-transplant allograft function (P = 0.03 and P < 0.05, respectively), however, not in the frequency of acute rejections’ episodes (P = 0.91 and P = 0.31, respectively).

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