
The role of pretransplant dialysis modality on renal allograft outcome

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Abstract
Background and objectives. The pretransplant dialysis modality might influence renal allograft and patient survival after transplantation. Studies published to date yielded conflicting results.

Methods. Deceased-donor allograft recipients reported to the 'Collaborative Transplant Study' were analysed, using multivariate Cox regression analysis, considering potential confounders which included pretransplant patient cardiovascular risk evaluation as well as immunological and treatment parameters. Primary end points were all-cause graft survival, death-censored graft survival and patient survival.

Results. In total, 60 008 recipients were analysed. Patients who were on peritoneal dialysis (PD) (n = 11 664) prior to transplantation demonstrated a 10% lower all-cause mortality (P = 0.014) but similar death-censored graft survival (P = 0.39) as recipients treated with haemodialysis (n = 45 651). This lower all-cause mortality in PD patients was primarily a consequence of a significantly lower rate of cardiovascular death with a functioning graft (P < 0.013) in a subcohort of patients defined as at increased risk.

Conclusions. Pretransplant dialysis modality per se has no significant impact on allograft outcome. Superior all-cause survival of PD patients is primarily due to a lower rate of cardiovascular death in a subcohort of high-risk recipients. This might explain the conflicting results published to date.

Introduction

Previous investigations have suggested that the modality of pretransplant dialysis might have an impact on subsequent renal allograft outcome and indicated an advantage of treatment with peritoneal dialysis (PD). As a possible

References


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explanation, delayed graft function was found to be less common in recipients transplanted after treatment with PD than in patients on haemodialysis (HD) [1–5]. On the other hand, at least in patients with early graft failure, acute graft thrombosis was more common in PD than in HD patients, suggesting that dialysis modality was associated with positive and negative effects [6–8]. Some reports have failed to demonstrate an influence of pretransplant dialysis modality on allograft and patient survival [1, 3, 9–11]. Most of the published studies have been limited either by relatively small patient numbers or by a lack of consideration of ‘death with a functioning graft’ and confounding risk factors. We used the large database of the international Collaborative Transplant Study (CTS) [12] to address the impact of pretransplant dialysis modality on allograft and patient survival.

Materials and methods

Study design

We conducted a retrospective cohort analysis of recipients of a deceased-donor kidney transplant performed during the time period 1998–2007 at transplant centers in Europe, North America, Australia and New Zealand. Only first transplants in adult recipients (≥18 years) were studied; multi-organ transplant recipients (for example kidney plus pancreas) were excluded.

Patient categorization

Expanded criteria donors (ECDs) were defined as kidney donors with one or more of the following donor characteristics: age ≥ 60 years, history of hypertension, non-heartbeating donor or considered ‘marginal’ by the transplant centre for other reasons.

Increased-risk recipients (IRRs) were defined as having a recipient age of ≥65 years or diabetes mellitus as the original disease leading to end-stage renal disease or a moderate or poor evaluation status as a candidate for transplantation as indicated by the transplant centre at time of transplant.

Statistical analysis and outcome

The primary end points were all-cause graft survival, death-censored graft survival (for which patients dying with a functioning graft were censored) and patient survival. Survival rates were calculated using the Kaplan–Meier method, and the log-rank test was used to compare outcome curves. Multivariate Cox regression analysis with back-step elimination was used to eliminate the influence of potential confounders. The following pretransplant factors were considered: original disease leading to end-stage renal failure; pre-existing diabetes mellitus; time on dialysis; year of transplantation; geographical region; recipient and donor sex, race and age; evaluation of recipient as a candidate for transplantation; evaluation of cardiovascular risk, extended donor criteria; human leucocyte antigen (HLA) mismatches; preformed panel-reactive antibodies and cold ischaemic preservation time. Rather than assuming a linear relationship, all metric confounders were included in the Cox regression model as dichotomous variables. For adjusted comparison of Cox regression incidence plots, the confounders were set to zero or the most frequent value. To take into account differences between PD and HD in special subpopulations, separate multivariate Cox regression analyses (considering the above-mentioned parameters) of different risk groups (taking into account IRR and ECD) were performed. In addition, the follow-up time period was partitioned into the first posttransplant year (taking into account IRR and ECD) and long-term follow-up (years 2–5). The years 2–5 to meet the proportional hazards assumption of the follow-up time period was partitioned into the first posttransplant year.

Results

In total, 60 008 deceased-donor kidney allograft patients were eligible for inclusion in the study. Demographics and baseline characteristics are summarized in Table 1. Recipients were categorized into four groups according to the pretransplant dialysis modality: PD (n = 11 664), HD (n = 45 651), the combination of both forms of dialysis (PD + HD; n = 1543) and no dialysis (preemptive transplantation, n = 1150). All baseline characteristics varied significantly between the groups and were therefore appropriately considered as confounders in multivariate analysis.

Kaplan–Meier survival estimates are presented in Figure 2. Unadjusted 5-year rates of graft survival (79.6 versus 76.1%, log-rank P < 0.001), death-censored graft survival (87.0 versus 85.2%, P < 0.001) and patient survival (89.6 versus 86.8%, P < 0.001) were all better in recipients on pretransplant PD than in recipients on pretransplant HD treatment. The 5-year rates for patients whose dialysis modality was changed from PD to HD prior to transplantation were similar to those of HD patients (Figure 1). The best 5-year success rates were observed in recipients with a preemptive transplant for graft (85.1%), death-censored graft (90.2%) and patient survival (92.3%), respectively (compared to all other groups P < 0.001).

Multivariate Cox regression analysis (considering original disease leading to end-stage renal failure; pre-existing diabetes mellitus; time on dialysis; year of transplantation; geographical region; recipient and donor sex, race and age; evaluation of recipient as a candidate for transplantation; evaluation of cardiovascular risk, extended donor criteria; HLA mismatches; preformed panel-reactive antibodies and cold ischaemic preservation time) revealed superior all-cause 5-year graft and patient survival in transplant recipients who had been on PD treatment as compared to patients on HD (P = 0.033 and P = 0.014, respectively) (Table 2), whereas no statistical difference was demonstrated for death-censored graft survival (P = 0.39). The relative risk for 5-year cardiovascular mortality posttransplantation of HD patients was 1.24 times higher [95% confidence interval (CI) 1.05–1.48; P = 0.013] than that of PD patients. For control purposes, we found that the mortality due to cancer did not differ between HD and PD patients (HD 3.7 versus PD 3.4%; P = 0.84). In addition to pretransplant dialysis modality, diabetes mellitus [hazard ratio (HR) 2.71; 95% CI 2.33–3.15; P < 0.001] and indication of increased cardiovascular risk during pretransplant evaluation (HR 1.46; 95% CI 1.17–1.83; P = 0.001) were shown to significantly contribute to cardiovascular mortality by Cox regression. Interestingly, when 5-year survival rates were analysed considering pretransplant risk categorization of recipient (IRR) and donor (ECD) as described in the methods section, multivariate Cox regression analysis showed superior 5-year graft (P < 0.001) and patient survival (P = 0.022) for PD recipients mainly in the subcohort of patients considered to be at increased pretransplant risk (IRR) who received allografts from ECDs (Table 2 and Figure 2).
follow-up separately, we analysed graft survival in the IRR–ECD group within the first year and between Years 2–5 after renal transplantation. Graft survival in the PD patient cohort was not only superior within the first year after renal transplantation (85.0 versus 80.9%, P < 0.001; HR 1.12) but also in the time period between Years 2 to 5 (78.8 versus 71.6%, P < 0.001, HR 1.38) (Supplementary Figure S1). In view of potential country-specific differences regarding indications and conditions of renal replacement therapy, we separately analysed graft survival for IRR–ECD patients from Europe and North America. We found a congruent superior graft survival of PD patients in Europe (P < 0.001) as well as in North America (P = 0.008). Additional analysis of death-censored graft survival revealed that the superior all-cause graft survival in the IRR–ECD patient group was due to better patient survival. In this subgroup, even though pretransplant cardiovascular risk evaluation showed a similar fraction of patients at increased risk in the two dialysis populations (HD 37.4 versus PD 37.2%, P = 0.95), consideration of multiple confounders (see Materials and methods) including pretransplant diabetes mellitus (HD 19.7 versus PD 25.2%, P < 0.001) and time on dialysis (median: HD 39 months versus PD 31 months, P < 0.001), revealed that mortality with a functioning graft due to cardiovascular death during the first five posttransplant years was significantly higher in HD patients than in PD patients (HR 1.67; 95% CI 1.16–2.40; P = 0.006). Deducted from the Cox regression analysis, Figure 3a shows the cumulative incidence of cardiovascular death with a functioning graft for a simulated IRR–ECD cohort of 60–64 year old diabetic male allograft recipients, adjusted for all potential confounders listed under Methods. To evaluate the influence of posttransplant renal allograft function, we analysed the cardiovascular death rate considering renal allograft function as a confounder in the Cox regression. The results showed that the cardiovascular death rate was increased (HR 1.92; 95% CI 1.24–2.97; P = 0.003). Figure 3b shows the adjusted curves for patients with a S-creatinine of <130 µmol/L at 3 months after transplantation.

**Discussion**

At first glance, our Kaplan–Meier analysis of >60 000 kidney transplant recipients supports the view that pretransplant PD is associated with better graft and patient survival and thus apparently agrees with observations from the USRDS database [13] and other studies [1, 3, 9–11]. However, after performing multivariate analysis in which multiple patient characteristics and immunological confounders,
as well as time on dialysis, year of transplantation, geographical region, pretransplant evaluation of the recipient as a candidate for transplantation and pretransplant evaluation of cardiovascular risk were considered, it emerged that only patient survival but not death-censored graft survival was superior in PD patients. The superior all-cause graft survival in PD patients was thus a consequence of a higher death rate in patients transplanted after treatment with HD. Aside from the necessity of analysing large patient numbers in order to reduce the element of chance, several additional aspects must be taken into consideration. First, almost one-half of renal allograft recipients die with a functioning graft and the evaluation of death-censored graft survival is therefore essential. Considering patient death with a functioning graft, the current opinion, that renal replacement therapy per se has an impact on allograft survival, could no longer be supported. This provides an explanation why our data, e.g. in contrast to the published non-death-censored USRDS registry data, did not demonstrate a superior graft survival rate in PD patients [13].

Secondly, to analyse these effects appropriately, prognostically important baseline characteristics as well as posttransplant renal allograft function must be taken into account. As demonstrated herein, baseline characteristics differed between the PD and HD groups and we therefore performed multivariate Cox regression analysis. We accounted not only for various demographics and comorbidities but also for pretransplant immunological parameters, as well as differences of geographical specifics in indications and circumstances of renal replacement therapy, time on dialysis, posttransplant allograft function and, most importantly, the evaluation of pretransplant cardiovascular risk. Furthermore, one has to consider not only the dialysis treatment modality applied immediately prior to transplantation but long-term treatment, including changes from one...
dialysis modality to another. Because a change of modality prior to transplantation might bias the results, we decided to form a separate group for those patients whose dialysis modality was changed. Our analysis shows that the better overall patient survival observed in PD patients is primarily a result of superior survival in the subcohort of PD patients at ‘high risk’ (patients considered at increased pretransplant risk who received allografts from ECDs). In other words,

![Fig. 2. Five-year graft survival rates according to recipient (increased risk recipient = IRR) and donor evaluation (expanded criteria donor = ECD) (see Materials and methods) and pretransplant dialysis treatment modality. a) no IRR, no ECD; b) no IRR, ECD; c) IRR, no ECD; d) IRR, ECD.](image1)

![Fig. 3. Adjusted incidence curves of cardiovascular death according to Cox regression performed on IRRs who received grafts from ECDs. All confounders listed under Materials and methods were considered. The incidence plots shown are representative for 60- to 64-year-old diabetic male allograft recipients (a) and in addition with a S-creatinine of <130 μmol/L at 3 months after transplantation (b).](image2)
particularly the high-risk recipients who were transplanted from increased-risk donors benefited from pretransplant PD treatment. Recognizing that country-specific differences in renal replacement therapy might bias the results, we separately evaluated graft survival for the IRR–ECD patient cohort in Europe and North America and observed a congruent superior graft survival of PD patients. Whereas differences in graft survival are usually most pronounced within the first year after transplantation, remarkably, our results revealed the strongest effect after the first year. This suggests an indirect long-term effect rather than a direct consequence of dialysis modality per se. The result of the patient subpopulation at increased pretransplant risk who received allografts from ECDs affects the overall patient survival rate and thus portends a general superiority of pretransplant PD treatment. After exclusion of the high-risk population, posttransplant survival of PD and HD patients was similar. This serves to illustrate why, in contrast to the USRDS registry report and in line with our observation, a recent analysis performed after exclusion of diabetic patients showed no survival advantage with respect to pretransplant dialysis modality [14].

What might be a plausible explanation for the superior survival of high-risk transplant recipients after PD treatment? Our investigation of cardiovascular death rates provides a clue. Although similar fractions of HD and PD patients in the IRR–ECD cohort were at increased pretransplant cardiovascular risk (HD 37.4 versus PD 37.2%, P = 0.95), and even though there was a significantly higher rate of patients with pretransplant diabetes in the PD group (25.2 versus 19.7%, P < 0.001), the highest rate of cardiovascular mortality was found in IRR–ECD patients after HD treatment (Figure 3a). This effect was verifiable even after adjusting for allograft function after 3 months (Figure 3b). However, the underlying mechanism leading to this observation is not easily understood.

We can only speculate that possibly residual renal function (RRF), which is believed to be better preserved in PD than in HD patients [15], might be responsible for the results since it has been shown that RRF has been associated with various effects influencing cardiovascular morbidity [16]. It is conceivable that high-risk patients are particularly vulnerable when loss of RRF occurs. However, this hypothesis remains speculative because RRF was not incorporated as a variable in the CTS database.

Our study has the limitation that, although the analysis carefully considered the influence of potential confounders as listed under Materials and methods, this was a retrospective cohort analysis and selection bias cannot be definitively excluded. In summary, giving appropriate consideration to pretransplant patient overall and especially cardiovascular risk evaluation, our data revealed that posttransplant allograft survival is not influenced by the pretransplant dialysis modality per se. The observed overall superior survival of PD patients was mainly a subpopulation effect. Mainly ‘high-risk patients who received kidneys from extended criteria donors benefited from pretransplant PD treatment in terms of better patients survival. These results suggest that particularly high-risk patients listed on the renal transplant waiting list might benefit from pretransplant PD treatment. Further studies are required to validate this hypothesis.

Supplementary data

Supplementary data is available online at http://ndt.oxfordjournals.org.

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