

ORIGINAL ARTICLE

Effect of dialysis modality on kidney transplant outcomes in South Africa: a single-centre experience

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ABSTRACT

Background: The effect of dialysis modality on transplant outcomes is disputed, with reduced long-term graft survival in patients receiving peritoneal dialysis reported in some studies. Resource constraints in South Africa limit patient choice of modality, with most state-funded units pursuing a policy of “peritoneal dialysis first”. Application of transplant eligibility as an entrance criterion for dialysis in these settings requires analysis of the effect of modality on transplant outcomes. We therefore undertook the first South African analysis of the effect of antecedent dialysis modality on the development of delayed graft function, rejection and graft function at long-term follow-up.

Methods: A retrospective review of all kidney transplants at Charlotte Maxeke Johannesburg Academic Hospital between 1 January 2006 and 31 December 2011 was undertaken. Graft outcome parameters (development of delayed graft function, graft function as indicated by eGFR, development of rejection, and graft survival) were compared between peritoneal dialysis (PD) and haemodialysis (HD) modalities using logistic regression and Cox proportional hazard modelling.

Results: Delayed graft function was more frequent in HD than PD recipients (66% versus 34%, $P = 0.004$); HD increased the odds of DGF independently of donor type (OR 3.82, 95% CI 1.46–9.99, $P = 0.006$). Graft function as indicated by eGFR was comparable between HD and PD subgroups on follow-up. Rejection was numerically more frequent in PD recipients (49% versus 35%, $P = 0.135$); PD was associated with an increased risk of rejection over 10-year follow-up (HR 3.32, 95% CI 1.40–7.91, $P = 0.007$). Overall, graft survival was not dissimilar between dialysis modalities ($P = 0.737$).

Conclusions: Haemodialysis may increase the risk of delayed graft function, possibly due to haemodynamic aberrations associated with this modality, as reported elsewhere. Peritoneal dialysis appears to be associated with increased risk and earlier occurrence of rejection, consistent with previous studies, suggesting accelerated immune reconstitution in this modality. Despite these associations, no effect was observed for dialysis modality on long-term graft function or survival, mirroring previous findings from the developed world.

Keywords: dialysis modality; kidney transplant; transplant outcomes; South Africa.

INTRODUCTION

Kidney transplantation is the preferred treatment for kidney failure (KF), offering improved mortality and morbidity and lower long-term cost compared to patients remaining on dialysis [1]. Declining rates of transplantation and increasing organ waitlists globally result in many patients receiving prolonged courses of dialysis prior to engraftment [2].

Lower staff and infrastructure costs to the healthcare system, greater preservation of economic activity, and reduced demand on individual patient finances to fund transportation render peritoneal dialysis (PD) an attractive kidney replacement therapy (KRT) for low- to middle-income countries [3]. As a result of resource limitations, KF patients in these settings may not have the

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choice of dialysis modality but may instead be accommodated on KRT programmes under a “peritoneal dialysis first” policy.

Although the effect of prescriber-determined modality assignment on dialysis outcomes has been well documented [4], the contribution of modality on outcomes after transplantation remains less defined [5–12]. In the South African context, access to KRT in the state-funded sector is rationed subject to transplant eligibility [13,14]. Given the declining rate of transplantation in the local and other settings [2,15], clarification of the effect of dialysis modality on transplant outcomes is urgently required in the light of such rationing.

We therefore sought to characterise the role of dialysis modality on graft outcomes in the local context. We analysed the effect of modality on delayed graft function (DGF), rejection, and overall survival over 10 years of follow-up.

METHODS

A retrospective review of all patients undergoing kidney transplantation between 1 January 2006 and 31 December 2011 at the Charlotte Maxeke Johannesburg Academic Hospital was undertaken. Dialysis modality was determined by recorded data at the time of transplantation and retrospectively validated by dialysis unit records; recipients who received both modalities for more than 3 months each were excluded from analysis. Baseline data (recipient age, sex, ethnicity, HIV infection status, comorbidity with diabetes mellitus, pre-engraftment dialysis modality, haemoglobin concentration, and panel reactive antibody percentage (PRA)) and data on outcomes (presence of DGF, graft function as determined by estimated glomerular filtration rate, time to first episode of rejection, and long-term graft survival) were anonymously extracted and stored on an Excel (Microsoft Corp., Redmond, WA, USA) database prior to export to Stata version 17.0 (StataCorp, College Station, TX, USA) for analysis. Permission to undertake this study was obtained from the Human Research Ethics Committee of the University of the Witwatersrand (protocol number M170954).

Baseline characteristics were compared between treatment modalities using Mann–Whitney U testing for continuous data and Fisher’s exact or Pearson’s chi-squared testing for categorical data, as appropriate. The development of DGF was defined as the requirement for dialysis within the first week of engraftment as per accepted definition [16]; simple logistic regression was used to model the effect of baseline characteristics on the odds of DGF.

Graft survival curves were fitted using the Kaplan–Meier method. The effect of baseline characteristics selected a priori and dialysis modality on rejection-free survival and overall graft survival were modelled using Cox proportional hazards.

RESULTS

Baseline characteristics of the sample cohort are shown in Table 1. No significant difference was detected between dialysis modality groups in this series. The cohort consisted of a preponderance of male patients (62.2%) of Black African ethnicity (78%); most patients (84%) received a deceased-donor transplant. Pre-sensitisation as evidenced by PRA was uncommon in the patients selected (median PRA 0%, range 0–90%). Standard induction therapy in this cohort included basiliximab, with antithymocyte globulin (ATG) reserved for recipients with PRA above 30%; only two recipients in this series fell within the latter range. All engraftments were from blood group-compatible donors with negative T-cell complement-dependent cytotoxicity assay. Most recipients in this historical cohort (87%) were maintained on a cyclosporine A (CyA)/mycophenolate mofetil (MMF) regime.

DGF occurred in 48 recipients (53%). DGF occurred almost exclusively among recipients of deceased donor grafts (96% of DGF episodes) and was more frequent in the haemodialysis (HD) cohort compared to peritoneal dialysis (PD) recipients (66% versus 34%, $P = 0.004$); prescription of HD was associated with an increased odds of DGF, which persisted after adjustment for deceased donor engraftment (Table 2).

Graft function at 3, 6 and 12 months, and at 5 years, showed no statistically significant differences between HD and PD cohorts (Table 3).

Rejection occurred in more PD recipients than in those receiving HD prior to transplant (48.6% versus 34.6%, $P = 0.135$); the number of rejection episodes among the PD group (median 0 episodes, interquartile range 0–2 episodes) was not significantly different from that among HD recipients (median 0 episodes, interquartile range 0–1 episodes, $P = 0.222$). Time to first rejection event was, however, shorter in the PD group (Table 4, Figure 1).

No difference in overall graft survival was detected between PD and HD groups (Cox–Mantel F test, $P = 0.737$). Time to graft loss showed no difference between dialysis modalities in Cox proportional hazards modelling (Table 5, Figure 2).

Table 1. Baseline characteristics of the sample cohort.

	Haemodialysis (n = 55)	Peritoneal dialysis (n = 35)	P value
Age (years)	40 (31–48)	45 (36–50)	0.111*
Sex			
Male	34 (62%)	22 (63%)	0.551**
Female	21 (38%)	13 (37%)	
Ethnicity			
Black African	43 (78%)	27 (77%)	0.974 ⁺
White	7 (13%)	5 (14%)	
Indian	4 (7%)	2 (6%)	
Mixed ethnicity	1 (2%)	1 (3%)	
Haemoglobin at engraftment (g/dL)	11.8 (10.3–13.4)	11.7 (11.1–12.4)	0.792*
Panel reactive antibody percentage	0 (0–0)	0 (0–0)	0.669*
Hypertensive	52 (95%)	33 (94%)	0.649**
Diabetes mellitus	2 (4%)	4 (11%)	0.156**
HIV positive	0	1 (3%)	0.389**
Donor type			
Deceased donor	43 (78%)	33 (94%)	0.116 ⁺
Related living donor	11 (20%)	2 (5.7%)	
Non-related living donor	1 (2%)	0	
Immunosuppression regime			
CyA/MMF/prednisone	47 (86%)	31 (89%)	0.493 ⁺
FK/MMF/prednisone	7 (13%)	3 (9%)	
CyA/AZA/prednisone	0	1 (3%)	
FK/AZA/prednisone	1 (2%)	0	

Values are n (%) or median (interquartile range).

Abbreviations: CyA, cyclosporine A; FK, FK506 (tacrolimus); MMF, mycophenolate mofetil; AZA, azathioprine.

*P as determined by Mann–Whitney U testing; **P as determined by Fisher's exact testing; ⁺P as determined by Pearson's chi-squared testing.

Table 2. Logistic regression: odds of developing delayed graft function.

	Unadjusted		Adjusted for donor type	
	OR (95% CI)	P value	OR (95% CI)	P value
Age (years)	0.99 (0.96–1.03)	0.902	0.98 (0.94–1.02)	0.366
Black African ethnicity	1.04 (0.37–2.91)	0.942	0.68 (0.22–2.10)	0.503
Male sex	2.70 (1.08–6.75)	0.034	2.13 (0.81–5.58)	0.123
Haemodialysis	3.08 (1.24–7.68)	0.016	3.82 (1.46–9.99)	0.006
Peritoneal dialysis	0.19 (0.07–0.54)	0.002	0.06 (0.02–0.26)	0.001
Haemoglobin pre-engraftment (g/dL)	0.92 (0.79–1.07)	0.267	0.89 (0.76–1.04)	0.139

Table 3. Graft function at follow-up.

	Haemodialysis	Peritoneal dialysis	P value
eGFR at 3 months (mL/min/1.73 m ²)	66.7 (46.1–94.1)	62.8 (46.7–81.4)	0.749
eGFR at 6 months (mL/min/1.73 m ²)	65.6 (39.1–84.7)	77.8 (53.6–96.9)	0.110
eGFR at 1 year (mL/min/1.73 m ²)	70.7 (51.2–86.5)	66.5 (48.6–99.8)	0.676
eGFR at 5 years (mL/min/1.73 m ²)	76.9 (57.9–97.3)	56.9 (44.2–92.2)	0.116

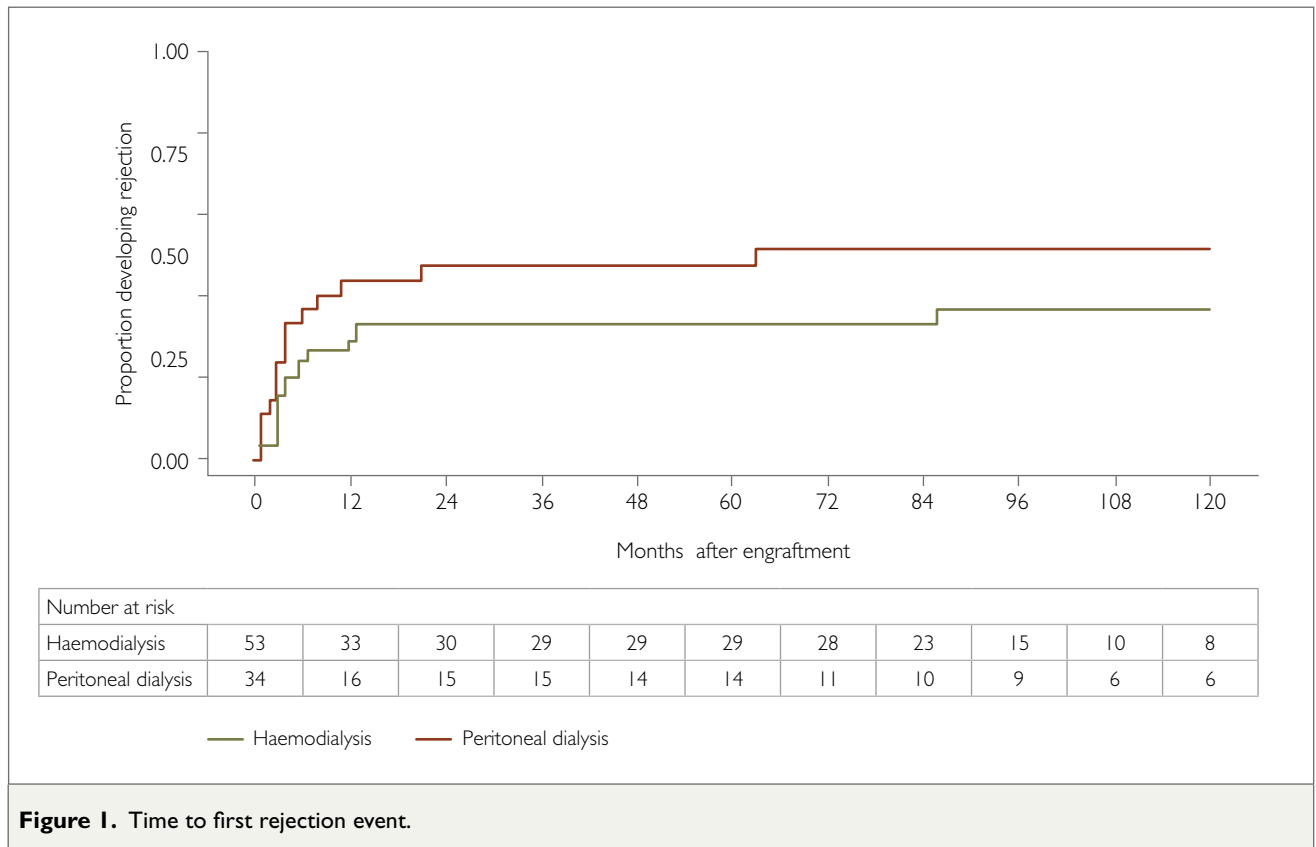
Values are median (interquartile range); P as determined by Mann–Whitney U testing.

Table 4. Cox proportional hazards model, time to first rejection event.

	HR (95% CI)	P value
Age (years)	0.99 (0.96–1.03)	0.917
Black African ethnicity	2.15 (0.72–6.39)	0.168
Male sex	1.50 (0.62–3.59)	0.365
Deceased donor graft	0.37 (1.03–1.35)	0.135
Panel reactive antibody percentage	1.01 (0.99–1.04)	0.242
Haemodialysis	0.30 (0.13–0.71)	0.007
Peritoneal dialysis	3.32 (1.40–7.91)	0.007
Delayed graft function	2.92 (1.17–7.29)	0.021

Table 5. Cox proportional hazards model, overall graft survival.

	HR (95% CI)	P value
Age (years)	1.01 (0.98–1.04)	0.474
Black African ethnicity	0.80 (0.38–1.69)	0.567
Male sex	0.94 (0.38–1.69)	0.865
Deceased donor graft	1.43 (0.44–1.99)	0.554
Panel reactive antibody percentage	0.99 (0.97–1.02)	0.668
Delayed graft function	2.82 (1.29–6.19)	0.009
Haemodialysis	0.90 (0.45–1.79)	0.767
Peritoneal dialysis	1.07 (0.54–2.15)	0.833
Rejection event	3.09 (1.59–6.03)	0.001



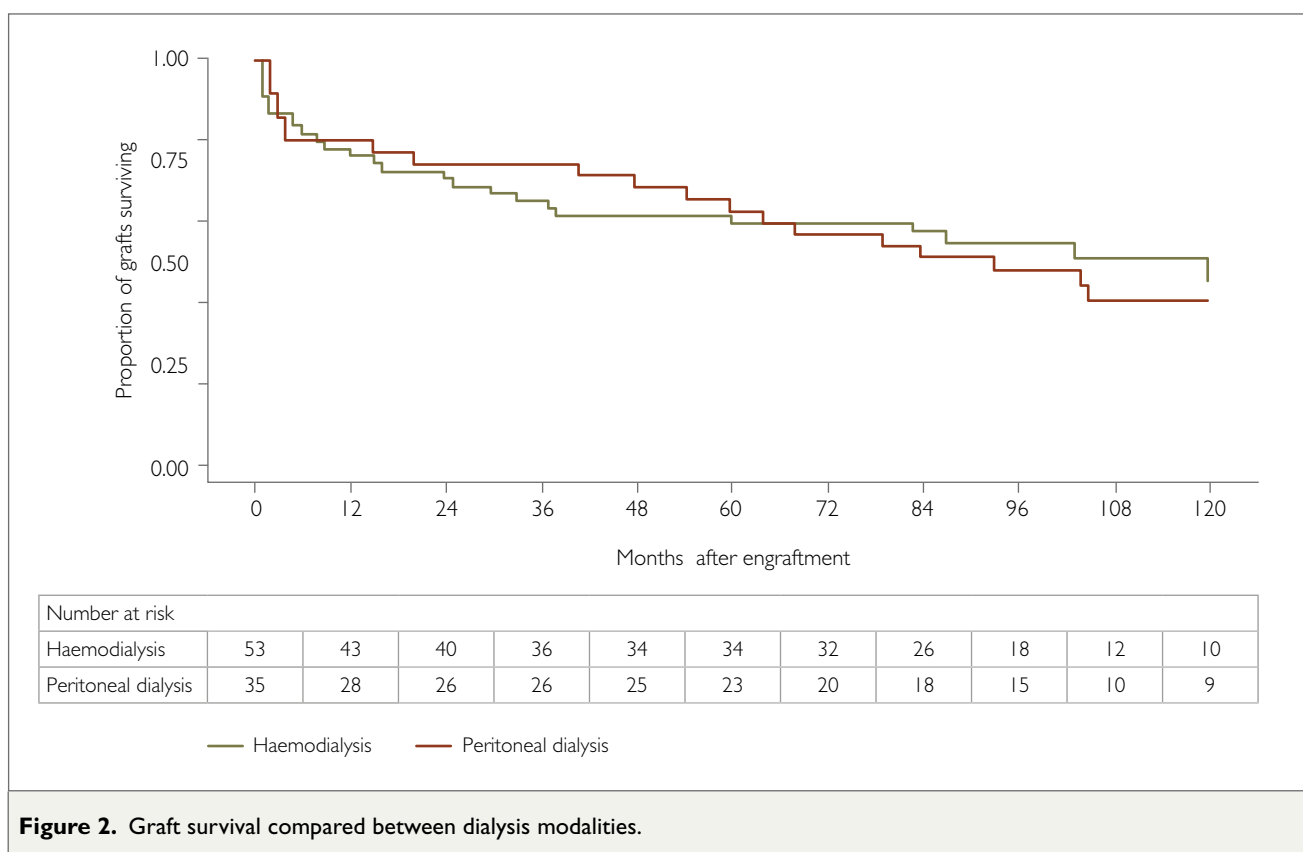
DISCUSSION

This first reported analysis of the effect of dialysis modality on transplant outcomes in the South African context shows no significant difference in long-term graft survival between modalities. As such, rationing of KRT access according to transplant eligibility is not on its own a contraindication to the adoption of “peritoneal dialysis first” policies in resource-limited settings.

Equivalent long-term graft survival in PD and HD recipients has previously been reported in North American,

European, and Australasian studies [2,6,7,9]. In contrast, other European and Asian series have suggested reduced long-term graft failure in PD recipients [8,10,11]. Short duration of follow-up, with few studies exceeding 5 years, limits interpretation of these findings. Goldfarb-Rumyantzev et al. [5], who analysed graft survival in patients followed for up to 11 years, reported increased risk of graft failure in HD recipients.

Higher rates of DGF have been reported in HD recipients by other investigators [6,8,9,11]. Relative recipient hypovolaemia arising from recent ultrafiltration exacerbating



graft ischaemic injury is the most commonly advanced explanation for this association [17], although additional factors particular to this dialysis modality may also contribute. For example, increasing HD vintage is known to exacerbate DGF risk in these recipients, even in living donor transplants [18,21]. Longer HD duration is associated with increased probability of pre-sensitisation, a known risk factor for DGF [18]. Although pre-sensitisation as evidenced by PRA was not dissimilar among PD and HD recipients in the present study, we cannot retrospectively exclude the possibility of non-panel antigen-directed antibody in our patients. Considering that HD patients enrolled in a “PD first” programme are likely to have been on dialysis for longer than those on PD, it is probable that both pre-renal and immunological factors underly the increased odds of DGF observed for HD recipients in this cohort.

As expected, the occurrence of DGF in this study was associated with an increased risk of subsequent rejection [20]. Somewhat counterintuitively given the previously noted associations with DGF, HD did not independently increase risk of rejection in the present study. A higher rate of rejection among PD recipients has previously been reported by Van Holder et al. [21]. Longitudinal follow-up of peripheral blood lymphocyte subsets from PD recipients has shown more rapid reconstitution of immune responsiveness, suggestive of greater preservation of immuno-

competence by the modality in comparison to those from HD patients [22]. Faster return to immunoreactivity may account for the shorter time to first rejection episode observed in our PD cohort.

Despite reductions in incidence under modern immunosuppression protocols, acute rejection episodes remain an important predictor of poorer long-term graft survival [23]. The increased risk of late period graft loss in patients experiencing DGF is well-described in the literature and appears to be independent of its association with subsequent rejection [24]. Instead, since the duration of DGF has been shown to correlate with risk of later graft loss [24,25], mechanical injury initiated during DGF may be an important factor in reduced survival [26].

Indeed, in the present study, rejection and DGF exerted an independent effect on long-term graft survival. A striking feature of this analysis is the similarity in hazard ratios for these factors in respect of this outcome parameter. Since HD in this cohort increased the risk of DGF and PD the risk of rejection, it is possible that any deleterious effect of one modality on graft survival was counterbalanced by a negative effect of similar magnitude exerted by the other. Additionally, any effect of dialysis modality on graft survival may have been ameliorated by multiple confounding factors which may have contributed to the development of rejection or DGF.

In this regard, we acknowledge that interpretation of the findings of the present study is subject to limitations. We did not include cold ischaemic time (CIT) or human leukocyte antigen (HLA) mismatch ratio as factors in our analyses due to the lack of uniformly available retrospective data for these parameters. Whereas CIT is a well-known contributor to DGF [27], its effect on rejection risk is less clear and may be a significant factor only in the latter if more than 24 hours [28]. Such prolonged CIT is unusual in the local setting and unlikely to have affected rejection outcomes. Considerable data provide evidence that implies an effect of HLA mismatch on rejection risk, although quantification of this risk is confounded by historical variability in HLA typing and antibody detection technologies [29]. It has been suggested that modern immunosuppression protocols have reduced the risk of rejection in HLA mismatched transplants except in highly pre-sensitised recipients [29]. Inclusion of PRA data therefore compensates for the lack of HLA mismatch data in the present study. The period of dialysis represents an additional potential confounder not fully accounted for in this study. Whereas earlier studies suggested poorer graft survival with prolonged waitlisting on dialysis, more recent work has failed to demonstrate this association being sustained [30]. Similar graft survival in modality subgroups in the present series and lower rejection risk in HD patients, who are likely to have received dialysis for longer than PD patients in this cohort, suggest lack of confounding effect of this parameter. Finally, we acknowledge that the single-centre nature of this study may limit the generalisability of our findings. However, we believe that this restriction facilitated homogeneity of transplantation protocols and recipient demographics, thereby limiting confounding variables.

CONCLUSIONS

This novel analysis of South African data shows a limited effect of antecedent dialysis modality on post-engraftment kidney transplant outcomes. Whereas haemodialysis may increase risk of DGF through hypoperfusion-mediated ischaemia/reperfusion injury, peritoneal dialysis may shorten time to rejection due to preservation of immunocompetence. Despite these differences, in our study graft function and long-term graft survival appear independent of dialysis modality. These findings provide reassurance for resource-restricted settings where choice of dialysis modality may be limited.

Conflict of interest

The authors have no conflicts of interest to declare.

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