Has the Expansion in Extended Criteria Deceased Donors Lead to A Different Type of DGF and Poorer Outcomes?

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Abstract
Objectives: There has been considerable change in the practice of deceased kidney transplantation in the past 15 years with more extreme phenotypes implanted. The impact of this change in clinical outcomes is unclear. The primary aim of this study was to determine whether the increased use of expanded criteria donors – note this is not ECD my be worth shortening this to eCD as opposed to ECD (extended criteria donors –ECD and donors after circulatory death - DCD) affected clinical outcomes, including the incidence and pattern of delayed graft function (DGF).
Methods and Materials: A retrospective analysis of 1359 renal transplants was performed in a single unit over the course of 15 years. The first 10 years of data (group 1) were compared with the subsequent 5 years (group 2). Patient and donor characteristics were recorded. Patient and graft outcomes were analysed at 6 months and 12 months post-transplant, in addition to serum creatinine and patterns of DGF (post-transplant times: on haemodialysis, to peak creatinine, for creatinine to half, for creatinine to fall within 10% of baseline).
Results: There was a significant increase in the percentage of eCD allografts used in group 2, with a significant increase in the incidence of DGF. Despite this, the clinical outcomes were better - serum creatinine measured at 1 year and the incidence of biopsy proven acute rejection was less than half group 1. Graft and patient survival at 1 year were the same in both groups. Cold ischaemic time (CIT) was significantly reduced in group 2. Regarding the pattern of DGF, group 2 eCD kidneys had a significantly lower incidence of Type 1 DGF and a significantly higher incidence of Types 3 & 4 DGF. Time for creatinine to half in both groups was the best predictor of a serum creatinine <180 at 1 year, confirming previous reports.
Conclusion: The increased use of eCD kidneys (DCD and ECD) has led to a higher incidence of DGF, however the pattern has shown that, in this group of patients, the requirement for haemodialysis has significantly reduced. Long-term outcomes have not been affected. The key marker of future allograft function remained the time for creatinine to half in both the older and more recent more extreme cohort.

Key words: *Transplant, Renal, Delayed graft function, Patterns, Outcomes*

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Introduction

Delayed graft function (DGF) following renal transplantation is a common phenomenon and may be an important prognostic indicator of future graft function[i]. Higher incidences have been attributed to the increasing use of donors from more expanded criteria (eCD), such as

extended criteria donors (ECD)[ii] and donation after cardiac death (DCD) donors. Various definitions of DGF have been described[iii] with the most cited describing it as "*the need for dialysis in the first week after transplant"*[iv]. Aitken et al. have described four patterns of DGF, namely (1) *a prolonged haemodialysis* (HD): a prolonged period of haemodialysis followed by a fall in creatinine; (2) *a single haemodialysis* (HD1): a one-off session of haemodialysis prior to fall in creatinine; (3) *a slow decline* (SD): an immediate reduction in creatinine followed by a slow decline with more than 7 days required for the creatinine to half; and (4) *slow rise then a gradual decline* (SR): initial rise in creatinine followed by a slow decline with more than 7 days for creatinine to half with no requirement for dialysis[v]. It seems likely that these clearly defined patterns reflect a complex interaction between the susceptibility of the organ from pre-donation morbidity, and donation processes themselves (e.g. cold ischaemic time). Over the past 10 years there has been considerable change in deceased renal transplantation with a trend towards more extreme phenotypes being implanted[vi] and in improving the processes of transplantation e.g. reducing cold ischaemic times. The aim of this study was to determine whether the increased use of eCD (DCD and extended criteria donors (ECD)) affected clinical outcomes, particularly the incidence, outcomes and patterns of delayed graft function (DGF).

Methodology

A retrospective analysis of 1359 renal transplants was performed in a single unit over the course of 15 years. The first 10 years of data (group 1) were compared with the subsequent 5 years (group 2). Data from group 1 had been previously analysed and published by Aitken et al[v].

Prior to relocation in 2015 to the Queen Elizabeth University Hospital, Glasgow, the renal transplant unit was based in the Western Infirmary, Glasgow. The unit itself, its catchment area and processes remain unchanged as a tertiary referral centre for the West of Scotland and serves an approximate 2.6 million people. Transplants performed in patients under the age of 18 years were excluded.

Donor and recipient demographic data were collated. The primary outcome measure was the pattern of DGF. Secondary outcome measures included cold ischaemic time (CIT), creatinine at 12 months post transplant and biopsy proven acute rejection (BPAR).

Extended Criteria Donor (ECD) kidneys were defined as those from donors aged 60 years or above or those aged between 50 - 59 years with at least 2 of the following co-morbidities: high blood pressure, serum creatinine >1.5 mg/dl, or death arising from a cerebrovascular accident (CVA).

Our definition of DGF was the requirement for haemodialysis or the serum creatinine failing to halve during the initial 7 days post- transplant.

Protocols were in keeping with guidelines as per 1975 Helsinki Declaration.

Results

762 patients underwent renal transplantation between 2001 and 2010. 597 patients were transplanted between 2010 and 2015 which represents a 56.7% increase in transplantation rate in group 2 – the more recent time group. This was largely due to the increase in the

number of DCD kidneys transplanted. ECD kidneys represented 21.3% of allografts in group 1 compared with 30.2% in group 2. The CIT was significantly reduced in the more recent time group 2 (Group 1. 13.47hr vs. 9.75hr in Group 2). BPAR was also significantly reduced in group 2 (22.4% vs. 11.1%). Further demographic data has been summarised in Table 1.

Table 1

	2000-2010 ALL	2011-2015 ALL	P-value		2000-2010 DGF'S	2011-2015 DGF'S	P-value
	%	%			%	%	
Total	**762**	**597**		Total	**190**	**195**	
LD	24.1	24.10	NS	LD	1.20	3.60	NS
DBD	70.6	48.1	<0.0001	DBD	75.4	46.70	<0.0001
DCD	5.1	27.8	<0.0001	DCD	24.2	49.20	<0.0001
OTHER				OTHER	0.1	0.51	NS
ECD	21.3	30.20	0.0002	ECD	57.8	42.60	0.0029
SCD	78.7	69.80	0.0002	SCD	42.2	57.40	0.0029
DONOR SEX (%m)	54.5	52.40	NS	DONOR SEX (%m)	52.4	46.20	NS
DONOR AGE	44.68	47.60	NS	DONOR AGE	48.2	51.50	NS
CAUSE OF DEATH				**CAUSE OF DEATH**			
TRAUMA	20.1	8.70	<0.0001	TRAUMA	18.7	7.70	0.0014
ICH	66.5	38.00	<0.0001	ICH	69.7	53.30	0.001
HYPOXIC	2.7	15.20	<0.0001	HYPOXIC	3.4	22.10	<0.0001
OTHER	10.3	38.00	<0.0001	OTHER	8.2	16.90	0.0102
CIT	**13.47**	**9.75**	<0.0001	CIT	**16.4**	**12.4**	<0.0001
RECIP				**RECIP**			
SEX (% M)	59.7	60.3	NS	SEX (% M)	54.7	53.8	NS
AGE	43.6	48.9	NS	AGE	48.6	51.90	NS
TYPE OF HD				**TYPE OF HD**			
PRE	17.3	18.4	NS	PRE	10.2	5.10	NS
HD	63.3	72.4	0.0004	HD	70.3	88.70	<0.0001
PD	18.2	8.7	<0.0001	PD	19	6.20	0.0002
FAILING TX	1.3	0.5	NS	FAILING TX	0.5	0.00	
PREV TX	21.5	10.1	<0.0001	**PREV TX**	25.8	15.40	0.0117
0	78.5	81.74	NS	0	74.2	85.13	0.0077
1	18	8.21	<0.0001	1	19.6	13.33	0.0973
2	3.1	1.84	NS	2	5.1	1.54	0.0508
3	0.4			3	1.3		
1 YR GRAFT survival	91.1	91.00	NS	1 YR GRAFT survival	82	89.20	0.0442
I YR PATIENT survival	97.9	96.00	0.0395	I YR PATIENT survival	97.1	94.90	NS
BPAR	22.4	11.10	<0.0001	BPAR	28.9	19.00	0.0229
CR AT 1YR	184.2	130.30	<0.0001	CR AT 1YR	223.5	153.1	<0.0001

Overall, 24.9% of group 1 vs. 32.7% of group 2 patients had DGF (p=0.0015). With regard the pattern of DGF in DCD kidneys, there was no significant difference in the incidence of Type 1, 2 or 4 DGF between the groups. There was, however a significant decrease in Type 3 DGF in group 2 (Table 2). With respect to ECD kidneys, there was a significant decreased incidence of Type 1 DGF in group 2 and a corresponding increase in Type 2 and 4 DGF in group 2. There was no significant difference in Type 3.

Table 2

	2000-2010 DCD (%)	2011-2015 DCD (%)	p value	2000-2010 ECD (%)	2011-2015 ECD (%)	p value
Type 1 (HD)	47.8	55.2	NS	80	43.4	<0.0001
Type 2 (HD1)	13	21.9	NS	9.1	33.7	<0.0001
Type 3 (SD)	30.4	11.5	0.0058	9.1	12	NS
Type 4 (SR)	8.7	11.5	NS	1.8	10.8	0.0076

Table 3 outlines the effect of pattern of DGF on 1-year graft and patient survival. In addition mean serum creatinine at 1 year is shown for each pattern and also for time on haemodialysis (t^{HD}), time for creatinine to half ($t^{½}$), time for creatinine to fall within 10% of baseline ($t^{10\%}$) and gradient of creatinine decline (Cr_{grad}). There was no association between the patterns of DGF with regard to graft or patient survival. The serum creatinine at 1 year was lower in all patterns of DGF in the more recent time period - group 2, but significance was only achieved in Type 1. In group 2, $t^{½}$ 10-15 days was associated with the highest serum creatinine at 1 year which differed from group 1 data for which the highest serum creatinine was found to be in $t^{½}$ > 15 days.

Table 3

	2000-2010	2011-2015	2000-2010	2011-2015	2000-2010	2011-2015
	1yr graft survival (%)	1yr graft survival (%)	1yr patient survival (%)	1yr patient survival (%)	Mean Serum Creatinine at 1 Year (µmol/L) ± SEM	Mean Serum Creatinine at 1 Year (µmol/L) ± SE
Pattern of DGF						
Type 1 (HD)	90.7	91.8	98.1	95.3	215.6 ± 192.3 (n=110)	155.84 +/- 47.5 (n=86)
Type 2 (HD1)	81.2	86.4	87.5	91.5	234.9 ± 222.0 (n=16)	161.1 +/- 63.6 (n=59)
Type 3 (SD)	90.5	87	95.2	95.7	182.9 ± 72.5 (n=24)	137.45 +/- 27.4 (n=23)
Type 4 (SR)	100	85.2	100	96.3	178.8 ± 63.0 (n=6)	139.87 +/- 31.6 (n=27)
tHD						
< 5	92.5	88.46	97	95.4	199.0 ± 15.9	150.63 +/- 51.1
5-10 d	84.4	94.74	95.6	94.74	250.7 ± 38.2	140.56 +/- 32.4
10-15 d	90.9	92.86	95.5	100	227.4 ± 40.0	188.46 +/- 58.5
> 15 d	88.9	85.7	100	92.86	270.0 ± 52.89	186.5 +/- 59.28
t½						
< 5	88.1	92	97	96	211.3 ± 26.0	120 +/- 36.7
5-10 d	90.9	89.36	96.4	95.74	211.4 ± 21.1	157.1 +/- 46.7
10-15 d	100	92.3	100	100	221.5 ± 45	240.8 +/- 75.4
> 15 d	87.5	75	93.8	87.5	300.6 ± 54.3	167.5 +/- 43.3
t10%						
< 5	100	100	100	100	196.0 ± 20.6	175 +/- 103.14
5-10 d	83.8	91.89	94.6	97.3	219.1 ± 32.8	125.0 +/- 27.7
10-15 d	89.2	92.68	97.3	95.1	265.2 ± 38.3	145.8 +/- 40.98
15-20 d	86.2	91.67	96.8	95.83	247.2 ± 39.8	164.72 +/- 40.38
> 20 d	95.3	91.67	97.7	91.67	189.4 ± 20.7	178.8 +/- 43.08
Cr grad						
0-50	90.5	90.2	97.3	95.8	280.5 ± 33.4	154.65 +/- 52.2
50-100	91.2	83.3	97.8	91.67	195.9 ± 34.2	142.3 +/- 40.48
100-150	89.2	100	96.2	100	189.7 ± 32.3	390

As was the case with group 1, patients with serum creatinine >180µmol/L at 1 year had longer t^{HD} and $t^{½}$ compared with those with serum creatinine levels <180µmol/L (Table 4). The same applied to Cr_{min} (best creatinine in the first 30 days after transplant) with higher levels being found in those with serum creatinine levels >180µmol/L. Significance was also found for $t^{10\%}$ and also Cr_{max} (maximum creatinine) with serum creatinine >180µmol/L at 1 year associated with higher levels respectively.

Table 4

	2011-2015	2011-2015	
	Creatinine at 1 Year < 180 µmol/L	Creatinine at 1 Year ≥ 180 µmol/L	p value
Mean tHD (d)	4.8037	8.3824	<0.01
Mean tpeak (d)	2.79	3.4118	NS
Mean t½ (d)	5.717	10.034	<0.0001
Mean t10% (d)	12.057	16.821	<0.001
Mean Crmax (µmol/L)	767.14	861.35	<0.05
Mean Crmin (µmol/L)	155	282.06	<0.0001
Mean Crgrad	32.19	33.94	NS

In group 1, t^{HD} $t^{½}$ and Cr_{grad} were found to be the best predictors of a serum creatinine ≤180µmol/L at 1 year[v]. In group 2, t_{peak} (time to peak creatinine) of 2.5days (sensitivity 58.5%, specificity 55.7%, area under the curve 0.60), $t^{½}$ 6.5 days (sensitivity 70.6%, specificity 70.8%, area under the curve 0.73) and $t^{10\%}$ 13.5 days (sensitivity 58.8%, specificity 64.9%, area under the curve 0.66) were the best predictors of a serum creatinine ≤180µmol/L at 1 year (Table 5).

Table 5

	2011-2015				
	Best Predictive Value	**Sensitivity (%)**	**Specificity (%)**	**Area Under the Curve**	**p value**
Mean tHD	2.5d	53.7	57.3	0.58	NS
Mean tpeak	2.5d	58.5	55.7	0.60	NS
Mean t½	6.5d	70.6	70.8	0.73	<0.0001
Mean t10%	13.5d	58.8	64.9	0.66	0.00476
Mean Crgrad	29.5d	53.7	53.4	0.51	NS

In order to further delineate the influence of DGF on long-term outcomes we compared group 2 SCD and ECD grafts which were either DCD or DBD. Of the 195 DGF patients in group 2 there were 41 SCD DBD (21%), 42 SCD DCD (21.5%), 35 ECD DBD (17.9%) and 31 ECD SCD kidneys (15.9%). The results are summarised in Table 6.

Table 6

	12mth Cr (+/- SEM)	12mth eGFR (+/- SEM)	Graft Surv (%)	Patient Survival	BPAR
SCD DBD	139.9 (+/- 9.2)	52.6 (+/- 3.2)	90.2	92.7	12.2
SCD DCD	124.5 (+/- 7.1)	56.9(+/- 3.0)	95.2	97.6	19.1
ECD DBD	178.7 (+/- 16.0)	40.9 (+/- 3.2)	88.6	94.3	20
ECD DCD	183.7(+/- 15.7)	36 (+/- 2.4)	90.1	93.5	22.6

Discussion

Given the rapid changes to the quality of organs offered for transplantation, the differing recipient profile, and the improvements in the transplantation processes, a surrogate marker of patient and graft outcome is desirable. DGF may be such a marker and thus we report the impact of practice changes on the patterns of DGF and their relationship to ultimate long-term outcomes.

This study has found that the pattern of DGF was different between the two earlier and later groups, however long-term outcomes have not been affected and indeed with respect to serum creatinine levels, at 1 year these have improved considerably. Interestingly, this study confirms that the key marker of future allograft function remained the time for creatinine to half in both the older and more recent more extreme cohort, reflecting the physiological capacity of the respective organs.

The relationship between ECD kidneys, DGF and long-term outcomes thereof has multi-factorial influences and it is difficult to determine with certainty the influence each factor plays. It has been well established the effect of CIT on DGF[vii] and it was encouraging to show that our CIT have significantly reduced. Despite this, the incidence of DGF has increased and it would be logical to conclude that the donor characteristics and type of donation (DCD/ DBD) contribute more significantly to the development of DGF than CIT. Conversely, the increased use of ECD kidneys has not affected one year outcomes and we hypothesise that the significantly reduced CIT may be the main reason for improving clinical outcomes, as this would be predicted to reduce physiological stress on the allograft.

The difference seen in the pattern of DGF is interesting. The overall trend is that in those patients who develop DGF, there is a reduced requirement of multiple haemodialysis sessions. This would appear to be the significant change in the pattern of DGF in ECD kidneys, the consequence of which has led to a proportionate change in the other types. With respect to DCD kidneys, the changes between groups 1 and 2 are less pronounced with no significant differences found for those requiring haemodialysis post-transplantation. This perhaps is less surprising as the major shift in the latter 5 years of the study has not been with regard to the quality of DCD kidneys, but rather toward the use of older kidneys hence the major changes seen are those in the ECD group.

The reduced incidence of BPAR in more recent times (group 2) is also encouraging but this is hard to explain with merely better matching of donor to recipient. Other factors seem unlikely to be sufficient to be the cause of this such as a slightly older age group, or no observable change in immunosuppression practice. It may be that a longer time on haemodialysis before transplantation may lead to a reduced immune-vigilance, but we do not have data on this currently.

We would conclude that the increased use of ECD kidneys has not negatively affected the short-term outcomes in these patients. It will be interesting to compare the longer-term outcomes of the ECD kidneys.

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