

Perigraft fluid collections after kidney transplantation: Does the type of donor (uncontrolled donation after circulatory death vs. donation after brain death) have a role?

Félix Guerrero-Ramos¹, Teresa Cavero-Escribano², Alfredo Rodríguez-Antolín¹, Amado Andrés-Belmonte², Juan Passas-Martínez¹, Ángel Tejido-Sánchez¹

¹Department of Urology, Hospital Universitario 12 de Octubre, Madrid, Spain

²Department of Nephrology, Hospital Universitario 12 de Octubre, Madrid, Spain

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Corresponding author

Félix Guerrero-Ramos
Hospital Universitario
12 de Octubre
Department of Urology
Avda. Córdoba s/n
28041 Madrid, Spain
felixguerrero@gmail.com

Introduction Perigraft fluid collection (PFC) is a common complication after kidney transplant. Its etiology is not clear and not all the causes have been identified. The influence of the type of donor has never been evaluated. Our aim was to compare the incidence, severity and management of PFC in recipients of grafts from uncontrolled donors after circulatory death (DCD) with normothermic extracorporeal membrane oxygenation (NECMO) versus recipients of grafts from donors after brain death (DBD).

Material and methods We conducted a retrospective cohort study of 300 kidney transplants performed in our center between 2007 and 2012. Patients were divided in two groups: 150 recipients of Maastricht II DCD graft and 150 recipients of the DBD graft. Incidence, severity according to Clavien scale and management were analyzed in both groups, and comparison was carried out using Chi-square.

Results Of the 300 kidney recipients analyzed, 93 (31.4%) suffered PFC, showing no difference between DBD (32.0%) and DCD (30.8%) groups ($p = 0.9$). Complicated PFC rate (defined as a PFC generating vascular compression, fever or urinary tract obstruction) was 22.9% in the DBD group versus 22.2% in the DCD group ($p = 1$); most complicated PFC were due to urinary tract obstruction (81%), with no difference between the groups ($p = 1$). Concerning Clavien scale, 78.5% of the PFC in our series were Clavien I, 19.4% Clavien IIIa and 2.2% Clavien IIIb, with no difference between both groups ($p = 1$).

Conclusions PFC is a frequent complication that appears in a third of our patients, showing no difference in the incidence or severity between DBD and uncontrolled DCD graft recipients.

Key Words: donation after brain death ↔ donation after circulatory death ↔ kidney transplantation
↔ normothermic extracorporeal membrane oxygenation ↔ perigraft fluid collection ↔ surgical complications

INTRODUCTION

Kidney transplantation is the best treatment for patients with end-stage chronic kidney disease, better than dialysis in terms of survival and quality of life [1, 2]. Furthermore, this has been demonstrated in all groups of patients and ages. The consequence of these results, which show a great superiority of kidney transplant over dialysis, has been an unprecedented growth in the organ demand [3, 4]. Despite the growing number of grafts from

live donors, the number of patients on the waiting list for a renal transplant continues increasing. One alternative to fight against this imbalance between available organs and the waiting list are kidneys from donors after cardiac death. Donation after cardiac death (DCD) is classified into controlled and uncontrolled [5]. Organs from uncontrolled donors have the highest ischemic risk due to factors as the hemodynamic instability inherent to cardiac death. Moreover, there are certain ethical issues related to this type of donation. These facts have not let

a proper expansion of uncontrolled DCD around the world [6]. However, in Spain this kind of donation is widely extended [7], and in our center we manage around 20–30% of uncontrolled DCD donors of our country. Graft preservation prior to recovery is usually performed with hypothermic extracorporeal membrane oxygenation; but in our center we use normothermic extracorporeal membrane oxygenation (NECMO).

Furthermore, kidney transplantation, as any other surgery, is not free from complications which can even lead to graft dysfunction [8, 9]. In general, complications after renal transplant are classified according to their origin: vascular, urological and surgical bed complications. Within the surgical bed complications, perigraft fluid collections (PFC) are one of the most frequent, with an incidence up to 50% depending on the series [10]. There is some controversy regarding these figures due to, among other reasons, the heterogeneity in the definition used. PFC by themselves are not serious, but can have important consequences in case of secondary infection, urinary tract obstruction or vascular compression.

Physiopathology of PFC is not clear and its etiology remains unknown. Moreover, the influence of the type of donor has never been studied, so we hypothesized that the different features of distinct kinds of grafts (ischemic damage, ischemia time, terminal serum creatinine) could have a role in PFC development.

Concerning the management of PFC, there are differing views on the need to systematically treat all the collections, being a regular topic of discussion in the transplantation forums [11]. Where different groups agree is in the crucial role of interventional radiology as the first therapeutic step, with resolution rates over 80% [12].

Our aim is to determine if there is a higher incidence of PFC in kidney transplantation with grafts from uncontrolled DCD with NECMO preservation than in kidney transplantation with grafts from donors after brain death (DBD). As secondary aims, we study if PFC in DCD kidney recipients have higher rates of complication or more severity and, hence, need more invasive procedures.

MATERIAL AND METHODS

We selected patients to carry out an observational cohort study with retrospective data collection with the following inclusion criteria: end-stage chronic kidney disease (either on dialysis – both hemodialysis and peritoneal dialysis – or on predialysis situation), heterotopic kidney transplantation performed in our center, maximum age of the recipient of 60 years, urinary diversion to bladder and re-

ipients of grafts from dead donors (either DBD or Maastricht II DCD). To identify these patients we queried the Hospital Universitario 12 de Octubre Kidney Transplantation Registry. We calculated a sample size of 294 patients to detect differences of up to 7% (alpha error 0.05 and statistical power 80%). Therefore, we selected 300 patients (150 received a Maastricht II DCD kidney under NECMO preservation and 150 received a DBD kidney) transplanted in our center between 2007 and 2012.

Preservation prior to organ recovery was done with NECMO; cold static preservation was used after organ recovery. Immunosuppression regime was according to our protocol: in general, for DBD recipients we use steroids, tacrolimus and mycophenolic acid; in DCD recipients we use steroids, rabbit anti thymocyte globulin (for induction) and mycophenolic acid, with late introduction of tacrolimus due to its nephrotoxicity. According to our protocol, every patient undergoes a graft ultrasound during the first week after transplantation.

Perigraft fluid collection was defined as the radiological finding (ultrasound or computed tomography) of abnormal serous content in the surgical bed, ruling out another complication as the cause (fistula, bleeding or abscess).

The following baseline characteristics were collected: donor and recipient age and gender, recipient age adjusted Charlson comorbidity index and cold ischemia time. We also collected PFC incidence, time of onset of the PFC and whether or not it was complicated. Complicated PFC has been defined as that inducing vascular compression, fever, pain or urinary tract obstruction (UTO). In our center, PFC are managed with periodic ultrasound until its spontaneous improvement, unless complication appears, in which case the first step is percutaneous drainage as soon as possible (in the first 24–48 hours after the diagnosis); if interventional radiology failed, the patient underwent surgical revision. We have collected, thereupon, the treatment required for PFC resolution and PFC stratification according to Clavien-Dindo scale [13].

Descriptive statistics (median and proportion) were used to describe baseline donor and recipient clinical characteristics and laboratory findings, as well as graft features comparing uncontrolled DCD and DBD kidney donors. Continuous variables were compared using Student's *t* test, while for non-normally distributed variables we used Mann-Whitney *U* test. Categorical variables were compared using Chi-square test.

Statistical analyses were performed using Stata version 12.0 (Statacorp LP, College Station, Tx, USA). All tests were two-sided, with *p*-values of <0.05 as the criterion for statistical significance.

RESULTS

Both groups were comparable regarding baseline characteristics (Table 1), except for donor serum creatinine (mg/dL), which was higher in the DCD group (1.3 vs. 0.8, $p < 0.0001$) and cold ischemia time, longer in the DBD group (1200 vs. 690 minutes, $p < 0.0001$). Median follow-up was over 4 years (53.4 months). Median age was 43 years for donors and 46 for recipients. In our series the incidence of PFC was 31.4% (93 patients), 32.0% in the DBD group (48 cases) and 30.8% in the DCD group (45 cases), with a median onset at the fourth postoperative day (interquartile range 2–27). No statistically significant difference was found in these parameters between both groups ($p = 0.900$ and $p = 0.359$ respectively).

Of the 93 patients diagnosed with a PFC, 21 (22.6%) were complicated, with no difference between groups

(22.9% and 22.2% in DCD and DBD, respectively, $p = 1$). However, complicated collections were diagnosed significantly later than uncomplicated ones (median 49 vs. 3 days, $p = 0.0012$), with no difference between DBD and DCD groups. Regarding complicated collections, most of them (81%) were due to UTO (Table 2).

Concerning management, none of the uncomplicated PFC needed intervention and they improved spontaneously, being followed up with ultrasound to rule out the onset of secondary complications. All the complicated collections were satisfactorily resolved with percutaneous drainage, except two patients, who underwent surgery after interventional radiology failure. Thus, 78.5% of PFC in our series were Clavien I, 19.4% Clavien IIIa and just 2.2% Clavien IIIb. No statistically significant difference between the two groups was found in respect to the management and Clavien stratification (Table 3).

Table 1. Baseline characteristics

Variable	DBD (n = 150)	uDCD (n = 150)	Total	p
Donor age, Me (i-r) years	44 (32–53)	41 (36–50)	43 (35–51)	0.542
Donor serum Cr, Me (i-r) mg/dL	0.8 (0.7–1.0)	1.3 (0.8–1.5)	0.95 (0.7–1.3)	<0.0001
Recipient age, Me (i-r) years	48 (37–54)	45 (38–53)	46 (38–54)	0.793
Recipient gender, n (%) male	100 (66.7)	92 (61.3)	192 (64)	0.336
Recipient BMI, Me (i-r) kg/m ²	26.1 (22.4–30.5)	27.3 (23.1–31.4)	26.9 (23.0–30.6)	0.111
High blood pressure, n (%)	112 (74.7)	107 (71.3)	119 (73)	0.516
Diabetes mellitus, n (%)	32 (21.3)	23 (15.4)	55 (18.4)	0.188
Cerebrovascular disease, n (%)	6 (4.0)	6 (4.0)	12 (4.0)	1
Coronary disease, n (%)	8 (5.3)	7 (4.6)	15 (5.0)	0.791
Peripheral vascular disease, n (%)	8 (5.3)	5 (3.3)	13 (4.3)	0.395
Charlson Index age-adjusted, Me (i-r)	3.2 (1.9–4.0)	2.9 (2.0–3.7)	3 (2–3.8)	0.517
Preop anticoagulant therapy, n (%)	7 (4.7)	4 (2.7)	11 (3.7)	0.357
Postop anticoagulant therapy, n (%)	12 (8.0)	18 (12.0)	30 (10)	0.357
Preop antiplatelet therapy, n (%)	38 (25.3)	28 (18.7)	66 (22)	0.163
Cold ischemia time, Me (i-r) min	1200 (1020–1380)	690 (585–870)	945 (660–1210)	<0.0001

Me – median; i-r – interquartile range; Cr – creatinine; n – number; BMI – body mass index; preop – preoperative; postop – postoperative; min – minutes

Table 2. Complicated perigraft fluid collection rate and causes of complication

Variable	DBD (n = 150)	DCD (n = 150)	Total	p
Complicated PFC, n (%):	11 (22.9)	10 (22.2)	21 (22.6)	1
Vascular compression, n (%)	2 (18.2)	2 (20.0)	4 (19.0)	1
Fever, n (%)	1 (9.1)	2 (20.0)	3 (14.3)	0.586
Pain, n (%)	0 (0)	2 (20.0)	2 (9.5)	0.214
Urinary tract obstruction, n (%)	9 (81.8)	8 (80.0)	17 (81.0)	1

*Percentages add up more than 100 because some patients had a complicated PFC due to 2 or more causes.

Table 3. Clavien-Dindo stratification and management of collections

Variable	DBD (n = 150)	DCD (n = 150)	Total	p
Clavien:				1
I, n (%)	38 (79.2)	35 (77.8)	73 (78.5)	
IIa, n (%)	9 (18.8)	9 (20.0)	18 (19.4)	
IIb, n (%)	1 (2.1)	1 (2.1)	2 (2.2)	
Treatment:				1
Watchful waiting, n (%)	38 (79.2)	35 (77.8)	73 (78.5)	
Percutaneous drainage, n (%)	9 (18.8)	9 (20.0)	18 (19.4)	
Surgery, n (%)	1 (2.1)	1 (2.2)	2 (2.2)	

Median size of PFC of our series was 50 x 26 millimetres (50 x 25 and 50 x 26 mm in the DBD and DCD groups respectively). Uncomplicated PFC were 45 x 24 mm in median, whereas complicated collections measured 90 x 60 mm (p = 0.0001).

There were neither deaths nor transplantectomies because of PFC in our patients.

DISCUSSION

We have analyzed the incidence of perigraft fluid collections in a series of 300 kidney transplants. Concerning baseline characteristics we have found differences in donor serum creatinine (higher in DCD donors), which is related to the ischemic damage secondary to the hemodynamic instability inherent to this type or death [14]. We have also observed a longer cold ischemia time in the DBD group, which is connected with the soon graft transplant surgery due to the deleterious effects on uncontrolled DCD grafts of the delay in the implant.

Overall incidence is 31.4%, with no difference between both groups. Nor did we find difference in the rate of complicated PFC or the severity of them between both groups. To our knowledge, this is the first series of renal transplantation with grafts from uncontrolled DCD donors with NECMO preservation in which PFC are studied. Besides, sample size is quite significant.

Perigraft fluid collections are among the most frequent complications after renal transplantation, showing an important variability according to the different groups. This is a consequence of the laxity in its definition; thereby, there are groups who consider it as a synonym of lymphocele, restricting the diagnosis of PFC to those collections that appear as an effect of the dissection prior to the implant, during which the breaking of lymph vessels can lead to the accumulation of lymph. Other authors also include in PFC hematomas and urine collections due

to fistula. However, it is estimated that most PFC are serous collections [15, 16, 17]. In the broader sense of the definition, PFC incidence after kidney transplantation is up to 50% [12]. In return, in the series where the definition has been restricted to lymphocele the incidence varies from 1.8% to 4.8% [18, 19, 20]. On the other hand, authors as Fonio [21] or Dubeaux [22] only consider PFC diagnosis in those patients who need active treatment, reporting an incidence of treated collections (both through percutaneous drainage or surgery) of 2.8% and 0.6% respectively.

In our series we have defined PFC as any radiological finding (by means of ultrasound or computed tomography) of pathologic fluid accumulate in the surgical bed, after ruling out potential causes that could make it secondary, as hematomas related to bleeding or urine collections related to urinary fistula. Therefore, we can consider our PFC as serous collections. With this in mind, the incidence of PFC in our series is 31.4%, similar in both groups. This diagnosis in one third of our sample is probably related to the fact that all our patients undergo a routine graft ultrasound during the first week after transplantation. Nevertheless, only 22.6% of PFC in our series were complicated (22.9% in the DBD group and 22.2% in the DCD group) – most of them (81.6%) due to UTO-. Therefore, one in every five PFC in our patients was subsidiary of active treatment according to our protocol.

In respect to the management of the collections, there is still certain divergence of views [23]. While there are groups that support treatment of all collections, other exclusively support the treatment of complicated PFC (due to compression of adjacent structures, overinfection or symptomatology) [16]. Anyway, all the authors agree that the first therapeutic approach should be percutaneous drainage whenever possible [21, 24], with success rates over 80% in most of the series [12].

In our series, interventional radiology achieved a success rate of 90%. Twenty patients were successfully treated with percutaneous drainage, and only two of them had to undergo surgical correction because of minimally invasive therapy failure. In the patients diagnosed with a non-complicated PFC, we decided watchful waiting, which has shown to be an adequate choice, given that spontaneous improvement was confirmed in successive control ultrasound examinations. The main limitation of this study is the retrospective design. We have used a simple and precise definition for perigraft fluid collection; however, we believe there is a limitation regarding comparison with other series due to the variability of this definition in the literature.

After the analysis and interpretation of our data, our algorithm is as follows. We perform routine ultrasound to every patient during the first week after renal transplantation surgery, not only to rule out PFC, but addressed to discard any abnormality of the graft and surgical bed. If the patient is diagnosed with complicated PFC, we recommend treatment as soon as possible (percutaneous imaging-guided drainage is the first choice, followed by surgery if it fails). If an uncomplicated PFC is found, we would recommend ultrasound follow-up after

1–2 weeks for those with a size over 50 millimeters, due to the higher risk of complications for those above this size. If shrinkage is confirmed, no further investigations are needed; on the other hand, if either renal function deteriorates or symptoms appear, new imaging tests should be performed. Just in the case that the PFC becomes complicated, it will need intervention.

CONCLUSIONS

We present a large comparative series of uncontrolled DCD kidneys, demonstrating that perigraft fluid collection is a quite frequent complication that appears in a third of our patients, showing no difference in incidence or severity between DBD graft and uncontrolled DCD graft with NECMO preservation recipients. Only complicated collections need active treatment; in this case, percutaneous drainage is the first step, keeping surgery for interventional radiology failure. Uncomplicated PFC do not need active treatment, and should be followed up with ultrasound until its improvement to rule out the onset of secondary complications.

CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

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