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REVIEW ARTICLE

Renal retransplantation: risk factors and results

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Abstract

Objective: To review our experience in renal retransplants.

Materials and methods: We carried out a retrospective study on 71 patients with retransplants between 1980 and 2005. We studied: the characteristics of the recipient and graft, surgery data, reasons for graft failure, number of rejects and transplantectomies and, survival of the graft.

Results: The most frequent reason for graft failure was chronic rejection. The causes of failure of the first graft were not associated with a greater loss of the second graft (p>0.05). The percentage of anti-HLA antibodies increased in the retransplant in comparison to the first (17.23±27.91% vs. 1.21±7.43%) (p=0.001), however, it was not correlated with a significant increase in loss of the second graft (p=0.320). There were no significant differences between the complications of the first and second transplants (p>0.05) and they were not associated with a loss of the graft (p>0.05). Patients with a transplantectomy in the first transplant an 8.5 times higher risk of undergoing a second transplantectomy (p= 0.0001 OR 8.54 IC 95%0.941 –77.501). The most frequent cause of transplantectomies in the retransplant was acute rejection. Acute rejection as a cause for transplantectomy in the first transplant proved to be an independent risk factor of transplantectomy of the retransplant (p=0.009). The mean survival of the second graft was 5.08±4.81 years, higher than the first transplant (p=0.133). The survival of the graft at 1.5 and 10 years was 83%, 75% and 52%, respectively.

Conclusions: The survival of the retransplant was not lower than the first, neither was there an increase in the number of complications.

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Retrasplante renal: factores de riesgo y resultados

Resumen

Objetivo: Revisar nuestra experiencia en retrasplantes renales.

Material y métodos: Se realizó un estudio retrospectivo de 71 pacientes retrasplantados entre 1980 y 2005. Se analizaron: características del receptor e injerto, datos de la intervención, causas de pérdida del injerto, número de rechazos y trasplantectomías y supervivencia del injerto.

Resultados: La causa más frecuente de pérdida del injerto fue el rechazo crónico. Las causas de pérdida del primer injerto no se asociaron con una mayor pérdida del segundo (p > 0,05). El porcentaje de anticuerpos anti-HLA incrementó en el segundo trasplante respecto del primero (17,23 ± 27,91% vs 1,21 ± 7,43%) (p = 0,001), pero no se correlacionó con un aumento significativo de pérdida del segundo injerto (p = 0,320). No existieron diferencias significativas entre las complicaciones del primer y segundo trasplante (p > 0,05) y no se asociaron con una pérdida del injerto (p > 0,05). Los pacientes con una trasplantectomía en el primer trasplante presentaban un riesgo 8,5 veces mayor de sufrir una segunda (p = 0,0001; OR: 8,54; IC 95%: 0,941-77,501). La causa más frecuente de trasplantectomía en el segundo trasplante fue el rechazo agudo. El rechazo agudo como causa de trasplantectomía en el primer trasplante se mostró como factor de riesgo independiente de trasplantectomía del segundo trasplante (p = 0,009). La supervivencia media del segundo injerto fue de 5,08 ± 4,81 años, superior al primer trasplante (p = 0,133). La supervivencia del injerto a 1, 5 y 10 años fue del 83, 75 y 52%, respectivamente.

Conclusiones: La supervivencia del segundo trasplante no es inferior al primero y tampoco existe incremento en el número de complicaciones.

Introduction

The therapeutic options of patients with terminal kidney disease include peritoneal dialysis, haemodialysis and kidney transplant, where the latter is considered as the treatment of choice in patients that qualify to undergo surgery. It has been proven that kidney transplant significantly improves the quality of life of patients and reduces mortality.[1,2] However, despite the improvement in survival of transplanted kidney grafts, many patients lose its function and are reinserted in dialysis programmes.[3-5] Of these, 32% of the patients return to the waiting list for a new transplant and 17% finally receive a retransplant. One fifth of the patients that lose the function of their graft die early mainly due to cardiovascular reasons, infections or neoplasias.[6,7] The rest of the patients were included in a waiting list for several reasons, such as the patient's own refusal or an unfavourable clinical condition. In spite of the increase in the health costs of performing a repeated medical-surgical procedure such as a kidney retransplant, it is still the best therapeutic option in this type of patient, given that it offers good cost-effectiveness, especially in the case of younger patients.[8]

Literature shows a lower survival rate of retransplants in comparison with survival of the first kidney transplant.[5,9-11] However, some series did not note any significant differences in short-term and long-term survival in them.[6,12-16] The association of different risk factors that affect the survival of kidney grafts in retransplants was studied by different authors,[14,16-20] however it must be borne in mind that there are different variables of retransplantation that do not appear in the first kidney transplant, such as the duration of the first graft, the period until the new transplant (retransplant), the origin of the graft of the previous transplant, the formation of anti-HLA antibodies following the loss of the graft or a history of transplantectomy.

Patients and methods

In the period between 1980 and 2005, a total of 1,170 patients underwent a transplant at the Fundació Puigvert. A retrospective study was carried out on those patients that had undergone a kidney retransplant on more than one occasion throughout their life. A description of the categorical variables studied is provided with absolute frequency and percentage, and the quantitative variables with the mean and standard deviation. We performed the comparison of the categorical variables between the first transplant and retransplant using the McNemar test, estimating the risk using the Odds Ration with a 95% confidence interval. We analysed the quantitative variables between the first transplant and the retransplant by means of a t-student test. We analysed the risk factors using the Chi-square statistical test and analysed the prognostic factors using a forward conditional binary logistic regression model. To study survival of the first transplant and retransplant, we carried out a Kaplan-Meier survival test expressing the result in mean and standard deviation with a 95% confidence interval. In all the cases, the approximation was bilateral and the significance level was the usual of 5% (α = 0.05). We used SPSS software (V 11.5) for the analysis.

Table 1   Characteristics of the donor, of the kidney transplanted and of the surgical procedure

	1st transplant	Retransplant
Mean donor age	42.83±21.50 years	43.96±17.54
Mean donor weight	67.24±16.90 kg	70.55±15.33 kg
Mean donor creatinine	93.71±23.90 mg/dl	84.78±30.50 mg/dl
Cold ischemia time	15.85±10.55 hours	16.11±9.07 hours
Donation type	Single organ (66.2%)	Multi-organ (59.1%)
Graft origin	Cadaver donor (82%)	Cadaver donor (87.5%)
Graft side	Right (67.5%)	Left (66%)
Implant location	Right iliac fossa (97.2%)	Left iliac fossa (97.2%)
Vascular anastomosis	External iliac (69%)	External iliac (89.2%)
Ureteral reimplantation	Extravesical (91.7%)	Extravesical (83.6%)

Results

Of the 1,170 patients operated on in the period under study, 71 received a transplant on more than one occasion. 69% of the recipients were men and the mean age was 35.28±13.44 years. In order of frequency, the aetiology of chronic kidney failure that led to the first kidney transplant in these patients was: glomerulonephritis (54.5%), tubulointerstitial disease (25.8%), nephrosclerosis (16.7%), renal polycystosis in 1 patient (1.5%) and others in 1 patient (1.5%). We failed to determine the cause of the chronic kidney failure in 5 cases. The number of HLA incompatibilities in these patients was 3.31±1.17 and the percentage of anti-HLA antibodies was 1.21±7.43%. The characteristics of the donor, the kidney transplanted and the surgical intervention points of references are described in table 1.

52/71 patients suffered acute rejection (73.2%) and 37/71 (52.1%) suffered chronic rejection. The complications of the first transplant are described in table 2. Four of the 8 patients that presented hematuria required endoscopic haemostatic revision for treatment. Of the patients with urinary fistula, three were treated conservatively. Two patients with ureteral stenosis had to be treated with open surgery after balloon dilatation failed. The kidney retransplant was performed at an interval of time of 7.16±4.90 years. Graft failure was were due to: chronic rejection in 35 patients (49%), acute rejection in 16 (22.5%), vein thrombosis in 12 (17%), recurrence of the disease in 3 (4%), vein stricture and haemorrhage in 2 patients each (3% respectively) and the presence of a non-viable kidney in 1 (1.4%) (fig. 1). Of the 71 patients, 29 (41%) required transplantectomy prior to the retransplant. Causes were vein thrombosis (31%), chronic rejection (31%), acute rejection (24%), vein stricture (7%) and bleeding from the surgical site (7%).

The interval of time until the graft failure was 3.80 ±4.56 years. The Kaplan-Meier analysis shows a functioning graft survival rate at one year of 59%, at five years of 32% and at 10 years of 12% The interval of time until the retransplant was 3.36±3.23 years. The number of HLA incompatibilities in the retransplant was 3.15±1.24 without there being significant differences with respect to the first transplant (p=0.316) and the percentage of anti-HLA antibodies was 17.23±27.91%, objectifying a statistically significant increase in relation to the first transplant (p=0.001); although it was not correlated with a significant increase in failure of the retransplant (p=0.320). Donor characteristics are described in table 1. There were no statistically significant differences in relation to the first transplant (p>0.05), except for the predominance of multi-organ donations and implantation in the left iliac fossa in the retransplant (p=0.009 and p=0.0001, respectively). We observed acute rejection in 24/71 patients (34%), objectifying a statistically significant decrease in relation to the first transplant (p=0.0001). Likewise, we observed chronic rejection in 15/71 patients (21%), which also decreased with respect to the first transplant (p=0.0001).

Table 2   Complications of the first transplants and retransplants

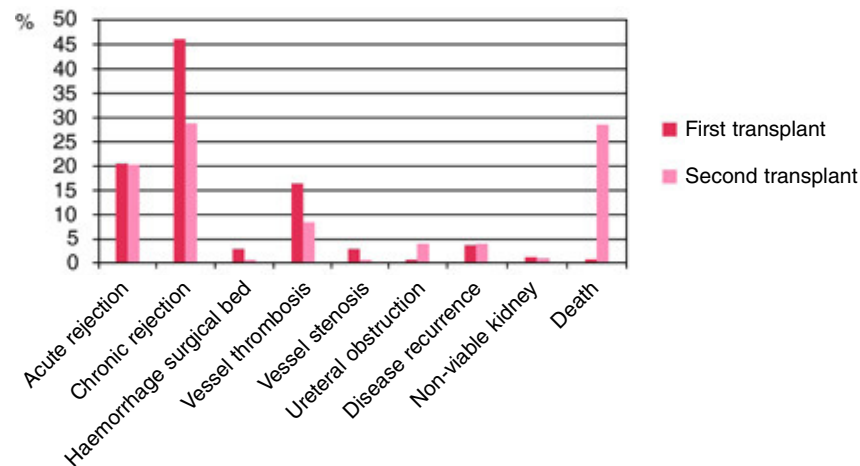|	1st transplant	Retransplant
Bleeding from the surgical site	11 patients (15.5%)	14 patients (19.7%)
Renal artery thrombosis	7 patients (9.9%)	2 patients (2.8%)
Renal vein thrombosis	4 patients (5.6%)	1 patient (1.4%)
Renal arterial stenosis	5 patients (7%)	4 patients (5.6%)
Lymphocele	13 patients (18.3%)	11 patients (15.5%)
Hematuria	8 patients (11.3%)	10 patients (14.1%)
Ureteral stenosis	5 patients (7%)	5 patients (7%)
Urinary fistula	8 patients (11.3%)	4 patients (5.6%)
Acute tubular necrosis	23 patients (32.4%)	28 patients (39.4%)
Wound hernia	3 patients (4.2%)	3 patients (4.2%)
Wound infection	4 patients (5.7%)	6 patients (8.5%)

Figure 1 Reasons for graft failure.

Complications during the retransplant are described in table 2; we did not observe any statistically significant differences in relation to the complications of the first transplant (p<0.05). In the univariate analysis, the complications were not associated with the graft failure (p>0.05). Five of the 10 hematurias in the retransplant required endoscopic haemostatic revision. All the urinary fistulas were treated without open surgery. Four of the patients with ureteral stenosis required open surgery as final treatment.

Of the 71 patients that underwent renal retransplantation, 22 (30%) suffered graft failure most frequently due to chronic rejection in 7 patients (32%), as occurred with the first transplant (p=1), and by order of frequency: death of the patient in six cases (27%), acute rejection in five patients (23%), vein thrombosis in two patients (9%) and recurrence of the disease and ureteral obstruction in 1 patient (4.5% respectively). We did not observe statistically significant differences in relation to graft failure of the first transplant (p>0.05 (fig. 1). In the univariate analysis, the different reasons for graft failure of the first transplant were not associated with a higher retransplant failure (p>0.05). Six of the 22 patients (36%) required transplantectomy. The patients that had undergone a first transplantectomy presented a risk 8.5 times higher of undergoing and second transplantectomy (p= 0.0001 OR 8.54 IC 95% 0.941–77.501),

although it was not associated with a higher graft failure rate in the univariate analysis (p=0.85). The most frequent cause of the second transplantectomy was acute rejection in 4 patients (67%) unlike in the first transplantectomy, in which the most frequent cause was chronic rejection (fig. 2). Acute rejection due to transplantectomy in the first transplant appeared to be a transplantectomy risk factor of the retransplant in the univariate analysis (p=0.001 OR 28.00 IC 95% 2.29-342.15); likewise, the binary logistic regression showed that acute rejection as the cause for a transplantectomy in the first transplant was a prognostic factor of a second transplantectomy (p=0.009).

The interval of time until the failure of the retransplant was 3.36±4.65 years without statistically significant differences with respect to the first transplant (p=0.926). The premature failure of the first graft was not associated to lower survival of the second graft (p=0.423). The mean survival rate of the second graft was 5.08±4.81 years, higher than the first transplant, at 3.80±4.56 years, although not statistically significant (p=0.133). The Kaplan-Meier analysis of the graft after one year was 83%, at five years it was 75% and at ten years it was 52% (fig. 3).

Of the 22 patients that presented failure of the second graft, 5 underwent a third retransplant within a period of time of 3±2.79 years and a single patient required a fourth graft. An increase in the percentage of antibodies similar to the second graft was objectified. In the majority of the cases, the right iliac fossa was chosen for the graft and an anastomosis at the level of the external iliac vessels was opted for. In 33% of the third grafts, we chose to perform an anastomosis with the common iliac vessels. Acute rejection was also the cause of graft failure in the third transplant as in the second graft. No transplantectomy was required in the third and fourth grafts.
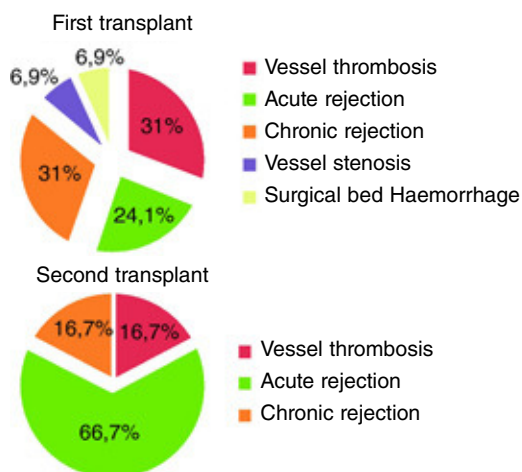
Discussion

The patients that underwent a kidney transplant with subsequent graft failure were included in a new dialysis programme. 32% of these patients returned to the waiting list for retransplants and 17% finally underwent the retransplant.[6] The mortality rate of the patients that

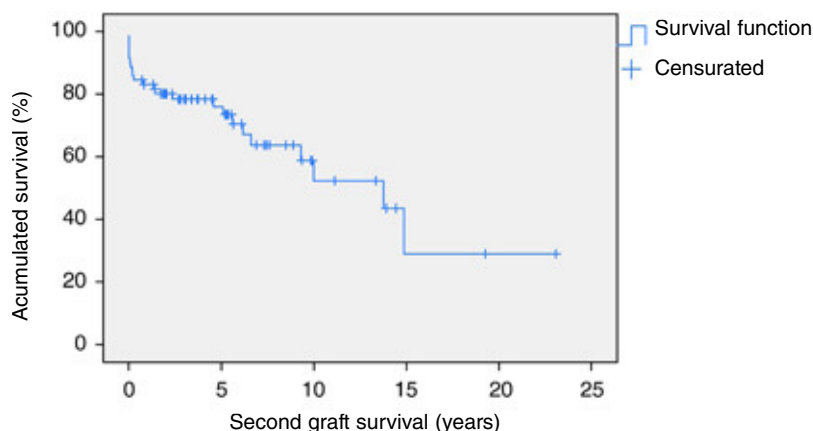**Figure 2** Reasons for transplantectomy.

Figure 3 Survival of retransplant.

underwent dialysis after graft failure was equal to the mortality rate of patients in dialysis that had not previously undergone a transplant, with the mortality rate increasing from 10-25 deaths per 1000 patients to 80 deaths per 1000 patients-year.[21] The survival of retransplants in relation to the first transplant shows disparate results according to the series published; thus, some studies mention lower retransplant survival rates[5,9-11] that contrast with a similar survival rate in other series.[12-16] The performance of retransplants represents a decrease in the risk of mortality, with improvement in the quality of life[1,21] and good cost-effectiveness, especially in young people.[8]

Different risk factors have been associated with worse survival of successive retransplants, including immunosuppression, the number of HLA incompatibilities, the percentage of circulating anti-HLA antibodies, donor type, occurrence of acute rejection, history of transplantectomy and the duration of the first graft.[14,16-20,22] Although some studies show a relation between re-exposure to non-compatible HLA antigens and lower survival of the graft,[16] the majority of the series do not note differences in the number of incompatibilities between the different transplants.[18,20,23]

In our study, the mean anti-HLA antibodies prior to the retransplant was 17%, significantly increasing with respect to the first.[24,25] Classically though, the increase in the percentage of anti-HLA antibodies prior to each transplant was associated with a decrease in the survival of successive retransplants,[26,27] in our experience, the increase in the percentage of anti-HLA antibodies does not influence the survival of the second graft. Unlike other series,[26] this increase is not associated with an increase in the number of acute rejections. The frequency of rejection in our series is similar to that of the literature,[11,13] lower than in the first transplant, and does not constitute a graft failure risk factor. Possibly the use of new immunotherapeutic regimens explains this difference with respect to older series.

The analysis of the characteristics of the donor, the recipient and the kidney transplanted does not show significant differences between the first transplant and retransplant, except for the predominance in multi-organ donations and greater use of the left iliac fossa in the retransplant.[11,28] The greater tendency to use the iliac vessels for the vascular anastomosis of the kidney graft in successive transplants is associated with an increase in the frequency of vein thrombosis in these retransplants,[28] even though in our series there were no significant differences as regards the frequency of thrombosis.[29]

We did not observe an increase in the frequency of complications in the retransplant or urological or vascular causes, nor causes related to the surgical wound.[16,28,29] The most frequent urological complication in retransplantation was macroscopic hematuria that required endoscopic revision in 50% of the cases. This was followed in frequency by ureteral stenosis and ureteral fistula, always located at distal level and which required open surgery in 80% of the cases. The most frequent vascular complication in retransplantation was bleeding from the surgical site (29%), followed by vein thrombosis that influenced graft failure. Neither vein thrombosis nor the rest of the complications of the first transplant are associated with greater failure of the second graft.

The reasons for failure of the first graft in our study were not risk factors for the loss of the second graft, which occurred in 30% as frequently as described in the literature.[14,30] The most frequent cause of failure of the second graft was chronic rejection (31%) and the second was patient death (27%).[5,14,31] We did not observe any significant differences from the rest of the causes of graft failure among the patients that survived. We performed a transplantectomy of the second graft in 36% with a similar frequency as in the first transplant. This frequency is higher than that published by Stratta et al. in retransplants,[32] however it is not associated with a higher graft failure rate. Moreover, the transplantectomy of the first graft was not a risk factor in the loss of the second graft, as mentioned in the literature.[18,30,33,34]

Acute rejection and vein thrombosis were the most frequent causes of transplantectomy in the second graft, while in the first transplant, the most frequent cause was chronic rejection.[35,36] Upon analysing the different causes that led to the first transplantectomy as risk factors for the failure of the second graft, acute rejection was considered in the multivariate analysis as an independent risk factor for another transplantectomy in the retransplant.

We accept that the interval of time until the loss of function of the first graft decreases the survival of successive

retransplants;[14,17,19,20,30,37] however, in our experience, the interval until the loss of function of the first transplant and retransplant was similar. Moreover, we did not associate the premature failure of the first graft to lesser survival of the second graft, contrary to what was previously published.[18,22,30,37] Literature provides confusing information regarding the survival of retransplants, which is around 81-96% per year, 69-88% at 5 years and 52-58% at 10 years.[5,9,10-16,38] In our study, graft survival was 83% at one year, 75% at 5 years and 52% at 10 years in accordance with the literature. Curiously, the mean survival of retransplants was higher than that of first transplants, although it was not statistically significant.

Conclusions

The performance of retransplants does not signify an increase in the number of complications. In patients with retransplants, despite the increase in anti-HLA antibodies, the mean survival did not decrease without there being differences between the reasons for graft failure. Those patients that underwent a transplantectomy due to acute rejection have a significantly higher risk of undergoing another transplantectomy in successive retransplants.

Conflict of interest

The authors declare that they have no conflict of interest.

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