

Case Report

Pre-Emptive Deceased-Donor Kidney Transplantation: A Extended Matched Cohort Study

Antonio Franco^{1*}, Patricio Más-Serrano², Yussel González¹, Elena de la Cruz¹ and Francisco Javier Pérez Contreras¹

¹Department of Nephrology, General University Hospital of Alicante, Spain

²Department of Pharmacology, General University Hospital of Alicante, Spain

***Corresponding author**

Antonio Franco, Department of Nephrology, General University Hospital of Alicante, Pintor Baeza 1, 03010 Alicante, Spain; Tel: 34699438342

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Keywords

• Pre-emptive renal transplantation; Deceased donor; Patient and graft survival; Dialysis; Psychological aspects

Abstract

Introduction: Kidney transplantation is the treatment of choice for patients with kidney disease who require replacement therapy. Dialysis is a step, but not mandatory prior to transplantation and pre-emptive transplant from deceased donors is possible.

Materials and methods: This is a retrospective, observational, matched cohort study. We compared 100 pre-emptive renal transplant recipients with 100 renal transplant recipients on dialysis both groups received a first renal graft, matched by age and gender of donors and recipients, time of transplant, immunological risk, immunosuppression and cold ischemia time.

Results: The percentage of recipients who presented early graft loss, delayed graft function and acute rejection was similar in both groups. No differences were observed in their renal function at 12 and 36 months after transplantation, as well as in the actuarial survival of patients ($p = 0.730$) and grafts ($p = 0.693$) in the studied period. The total calculated cost of the period on dialysis for the dialysis group was 12,172.565 Euros.

Conclusions: Pre-emptive transplantation can achieve comparable outcomes to those for post-dialysis kidney transplantation, and better quality of life with a reduced cost.

INTRODUCTION

Chronic kidney disease (CKD) causes significant morbidity and mortality, especially cardiovascular [1]. CKD is divided into stages from least to most severe [2]; stage 5 is the situation to adopt a series of strategies of treatment including the start of renal replacement therapy which will not only keep the patients alive, but also, at least in part, will maintain their quality of life.

Usually, patients are initially included in a dialysis program, either hemodialysis or peritoneal dialysis [3]. Both treatments are effective to maintain the patient alive; but they require prior surgical procedures, either an arterio-venous fistula, insertion of a central venous or a peritoneal catheter [4,5]. Moreover, these replacement treatments are far from effective and we only achieve partial restoration of the lost renal functions [6].

At the present time, we have one effective and complete treatment for CKD. So kidney transplantation is the treatment of choice in most patients with end-stage CKD [7,8]. Renal transplantation restores the patient's previous health condition, since the transplanted kidney fully replaces the functions lost by the native kidney; therefore the benefit/risk ratio is positive. However renal transplantation requires chronic pharmacological immunosuppression, which promotes opportunistic infections [9] and the incidence of cancer increases [10,11].

Usually, deceased-donor kidney transplantation is considered when the patient is already on renal replacement therapy.

Dialysis is generally a necessary, but not a mandatory step before kidney transplantation in patients who are candidates for this procedure. It is possible to have kidney transplantation without prior dialysis. This procedure is known as a pre-emptive, or pre-dialysis kidney transplantation, a reality in recipients from living donors [12], although it remains controversial in the case of deceased donors due to the lack of organs [7,8,13]. In France, pre-emptive deceased-donor kidney transplantation has been incentivized in recent years, with an increase from 5.6% to 15.5% between 2007 and 2014, with good results [14].

In 2007, our center started a pre-emptive deceased-donor kidney transplant program. It should be noted that patients in a pre-dialysis situation only receive a graft if there is no candidate for transplant on renal replacement therapy. We reported the results of this program in 2020 [15].

The objective of this study is to evaluate the results of our experience in pre-emptive, deceased-donor kidney transplantation with more recipients enrolled and a longer follow-up period.

MATERIAL AND METHODS

This is a retrospective and observational study with matched cohorts. Recipients who received a renal transplant from a brain dead donor at our Hospital between 2007 and 2016 were included. Two groups were defined: a pre-dialysis group (pre-dialysis patients who received a pre-emptive, deceased-donor

transplant) and a control group (patients on renal replacement therapy who received a first transplant from a deceased donor).

In the pre-dialysis group, patients had a glomerular filtration rate under 15 ml/min (measured by CKD-EPI), an estimated time to start dialysis under 6 months, and more than one year of follow-up after transplantation. Each case in the pre-dialysis group was matched by age and sex of donor and recipient, percentage of donors over 60 years, cold ischemia time, the blood group of the recipients as well as by transplant date. So the time between the dates of the transplantation of the pre-emptive recipient and the control was less than 7 days.

The immunological status of the recipients was evaluated via donor-recipient compatibility and the preformed antibody level and was similar in both groups.

The general immunosuppressive regime at the time of the kidney transplantation consisted of tacrolimus (initial dose: Advagraf® 0.2 mg/kg per day; subsequent doses were adjusted to maintain a trough concentration of tacrolimus between 8 and 10 ng/mL during the first month and afterwards between 6 and 8 ng/mL), mycophenolate mofetil (500 mg/12 h orally), basiliximab or timoglobulin in high-risk patients and a tapered corticosteroids regimen.

The variables evaluated were incidence of early graft loss (before 48 h), acute rejection (sudden alteration in graft function or presence of delayed graft function, with specific histological changes), delayed graft function (dialysis in the first week post-transplant), kidney function at 12 and 36 months (serum creatinine level), and graft and patient survivals at 1, 3 and 10 years.

The period of time in the transplant waiting list in each patient group was evaluated. Adherence to treatment was studied in both groups with the variation in the trough tacrolimus concentration (calculated as the mean of the coefficients of variation [CV] of the trough tacrolimus concentration for the individual patients obtained from month 3 through month 24 post-transplant, expressed as a percentage) along with a personal interview conducted at every visit.

CV (%) Standard deviation x 100

Mean

The theoretical cost resulting from the care of the patients on dialysis of the control group patients was quantified according to the study conducted by Arietta et al., [16]. The cost per patient on dialysis was calculated as the result of months on dialysis multiplied by monthly cost depending on the technique.

Statistical study

The continuous variables are expressed as the mean 95% confidence interval, or median and interquartile range (p25–p75), depending on the distribution type. The categorical variables are described as the number of percentage of patients by response category.

The continuous variables were compared between groups with Student's T-test or Mann-Whitney's U test depending on the

type of variable distribution. Categorical variables were analyzed using Fischer's test.

A survival analysis (Kaplan–Meier) was performed to analyze the percentage of patients and grafts lost during the follow-up period. Both groups were compared using the statistical test (log-rank). The level of significance was 0.05. The statistical analysis was performed with the SPSS software, version 24.

RESULTS

One hundred (100) recipients were included in the pre-dialysis group, matched with 100 patients in the control group, 75 of them on hemodialysis and 25 on continuous outpatient peritoneal dialysis. The less period of follow-up was 3 years post transplant. The median follow-up (months) in the pre-dialysis and control groups was 74.0 (p25–p75: 24.0–122.0) and 76 (p25–p75: 28.8–128.3), respectively. The time on the waiting list was similar in both groups (median in months: p25–p75; 4 [2–7] vs. 6 [2–11] months; $p = 0.100$).

No significant differences were observed between the groups in the age and sex of the donor and recipient, percentage of donors over 60 years, cold ischaemia time, and patients who received induction with thymoglobulin or basiliximab. No significant differences were also observed in the blood group of the recipients or their immunization status. The variability in the trough tacrolimus concentration was similar in both groups, with no lack of adherence detected during the interviews. Table 1 shows the similarity of the variables in both groups.

In the pre-dialysis group, the incidence of delayed graft function was similar to the control group (19.2 vs. 13.5%, respectively; $p = 0.426$). Similarly, no statistically significant differences were found between the two groups for the presence of acute rejection (pre-dialysis group: 10.1% vs. control group: 9.1%; $p = 0.809$) and early graft loss (pre-dialysis group: 5.2% vs. control group 7.1%; $p = 0.800$). Kidney function, evaluated by median serum creatinine, was similar in the pre-dialysis and control groups at one year (1.57 vs. 1.60 mg/dL, respectively; $p = 0.428$) and 3 years (1.74 vs. 1.62 mg/dL; $p = 0.335$) (Table 1).

Recipient survival at 1, 3 and 10 years was 94.1% 93.1% and 71.2% in the pre-dialysis group and 96.0% 89.7 and 74.1% in the control group, respectively ($p = 0.730$)

Similarly, graft survival in the pre-dialysis group was 90.4% at one year, 88.1% at 5 years and 62.8% at 10 years, and in the control group it was 92.3% at one year, 79.6% at 5 years and 61.7% at 10 years ($p = 0.693$).

The mean recipient survival time was not different in the pre-dialysis and control groups (126.8 [95% CI: 113.8–139.8] vs. 123.1 [95% CI: 109.7–135.5]) months, respectively; $p = 0.730$). Nor were significant differences in the graft survival time observed between the two groups (pre-dialysis group: 114.6 months [95% CI: 99.1–130.2] vs. control group: 109.3 months [95% CI: 93.7–124.8]; $p = 0.693$).

According to the total time on peritoneal dialysis (556 months) and hemodialysis (2697 months), the total cost of renal replacement therapy in our patients was 12,172.565 Euros.

Table 1 – Demographic data of the patients included in the pre-dialysis group and control group.

	Pre-dialysis group	Control group	p
Donor age (years), mean (95% CI)	53.2 (50.4–56.0)	53.1 (50.9–56.0)	0.965
Recipient age (years), mean (95% CI)	52.6 (49.9–55.3)	53.1 (50.8–55.4)	0.791
Donor sex (%M/F)	62.1/39.9	54.1/45.9	0.384
Recipient sex (%M/F)	67.0/33.0	64.1/35.9	0.665
Donor >60 years (%)	28.8	28.8	1.000
Cold ischaemia time (hours), mean (95% CI)	17.4 (16.6–18.4)	17.2 (16.2–18.1)	0.813
Thymoglobulin (%)	56	60	0.567
Basiliximab (%)	12	16	0.415
Cp TAC Variability; CV (%), median (p25-p75)	24.1 (19.5–33.0)	26.1 (19.1–44.1)	0.602
Blood group			0.520
A	56.1	50	
B	9.1	9.1	
AB	10.6	6.1	
O	24.2	34.8	
HLA incompatibility			0.862
4–6	64.5	61.5	
0–3	35.5	38.5	
PRA >50%	0	4.5	0.244

Cp TAC: trough tacrolimus concentration; CV: coefficient of variation; HLA: histocompatibility antigens; 95% CI: 95% confidence interval; PRA: panel-reactive antibody; M/F: male/female.

DISCUSSION

The worldwide experience with pre-emptive, deceased-donor kidney transplantation is hard to find and under debate [17]. Some authors have reported that the time on dialysis before kidney transplantation has a negative impact on its outcome, therefore performing it pre-emptively would be associated with greater graft and recipient survivals as compared to patients who remained on dialysis for some time [3,6,8,17-19]. Studies by Roake et al. [3] and Papalois et al. [19] have demonstrated superior survival in pre-dialysis recipients. These results were recently supported by a French multi-center study by Prezelin-Reydit in which it was concluded that pre-emptive transplant is associated with a lower risk of graft failure. Nevertheless, this conclusion may be questionable, because the dialysis group was older, with more cardiovascular co-morbidity, with a higher percentage of patients with diabetes mellitus than the pre-emptive group, and the donors were also older [20]. Other authors such as Luo et al. recommend this type of transplant, since they improve the patient's quality of life and reduce the economic cost, although they did not observe significant differences in terms of recipient or graft survivals. However, these authors did show evidence of a decreased rate of acute rejection [21].

In our study, as reported by Luo et al. [21], we did not find significant differences in recipient and graft survival rates. Foucher et al. reported the same conclusion in a recent study designed with a control group of more than 500 patients included in the waiting list for at least 6 months before their first dialysis session; in addition, they used an inverse probability score to make the groups more homogeneous. Nevertheless, the dialysis

group had a significantly higher percentage of hyperimmunized patients that were treated with more immunosuppression, which could alter the results [22].

The percentage of recipients who experienced acute rejection was similar in both groups (Table 2), which contrasts with the previously mentioned study by Luo et al. and other studies reported in the literature, which show that a longer time on dialysis increases the risk of rejection [21]. The study by Cacciarelli, with 325 kidney transplants, concluded that the incidence of acute rejection was lower in patients who remained on dialysis for a period less than 6 months [18]. In contrast, it has been proposed that patients who have not experienced the symptoms of CKD or the morbidity associated with dialysis may be less compliant with the immunosuppressant treatment [23], which would lead to a higher incidence of rejection. There was no evidence of any compliance in our group of recipients with pre-emptive transplant such as the results obtained by Papalois, who did not find a higher rate of non-adherence to treatment in patients who received pre-emptive kidney transplant [19].

Kidney function at 12 and 36 months after the transplantation was similar in both groups. However, in other studies, a higher rate of delayed kidney function in patients who were already on dialysis has been reported [17]. The hypothesis proposed is a higher inflammatory status, as well as an inadequate clearance of certain metabolites in these patients [24].

Foucher et al., exhaustively reviewed the ethical justification for transplanting patients in a pre-dialysis situation, which could lead to a longer time on the waiting list for patients on dialysis. In this study, the recipients from the dialysis group were on the

Table 2 – Efficacy and safety variables in the pre-dialysis group and control group (p25–p75: 25th and 75th percentile of the median).

	Pre-dialysis group	Control group	p
Delayed graft function (%)	19.2	13.5	0.426
Acute rejection (%)	10.1	9.1	0.809
Early graft loss (%)	5.2	7.1	0.800
Serum creatinine at 12 months, median (p25–p75) mg/dL	1.5 (1.4–1.6)	1.6 (1.4–1.7)	0.428
Serum creatinine at 36 months, median (p25–p75) mg/dL	1.7 (1.5–1.9)	1.6 (1.5–1.7)	0.335

waiting list for a mean time of 38 months, significantly longer ($p < 0.0001$) than the pre-dialysis group, with a mean time of 14 months [22]. Our experience is different, since the time on the waiting list in our patients is much shorter and it was not significantly different between the pre-dialysis and dialysis group: 4 and 6 months, respectively; therefore it was considered that, in our case, performing a pre-emptive; deceased-donor transplantation does not constitute an ethical dilemma.

As for the economic cost, it is worth to mention that renal replacement therapy (hemodialysis, peritoneal dialysis, and kidney transplantation) spends a 2.5% of the National Health System's budget and more the 4% of that for Specialised Care. The mean cost of hemodialysis, peritoneal dialysis, and kidney transplantation first year is 46,660, 32,432, and 47,136 Euros per patient per year, respectively. However, in subsequent years, the cost of the kidney transplantation decreases considerably: 6477 Euros per patient per year; renal transplantation is the technique with the best cost-effectiveness ratio [16], therefore we can affirm that it not only prolongs life, but that as far as the economic cost it is also a more advantageous option as compared with long-term dialysis [25]. Thus, the time on dialysis for the recipients in the control group entailed a cost which could have been reduced in the case of pre-emptive transplant. This is an objective data which should be added to the subjective benefit for the patient by avoiding dialysis and, prior to this, the proceedings needed before starting dialysis. However, it is necessary to point out the limited grafts available from deceased donors [3,8,17], a fact which would significantly limit the implementation of the proposed strategy.

The strong point of our study is in the analysis of the variables studied. So matching were made between pairs of recipients (pre-dialysis situation vs recipients already on dialysis) who were transplanted with a narrow time margin (under 7 days); whereas in the other referenced series [3,17-19], the group of recipients in a pre-dialysis situation constituted a sub-group of their transplant populations, without matching in terms of transplant time.

The weak point of this study is the limited number of enrolled patients and the follow up period could be longer.

CONCLUSION

In Conclusion, deceased-donor kidney transplantation offers patients in a pre-dialysis situation outcomes which are at least comparable to those of recipients on dialysis and prevents the morbidity, mortality and psychological impact derived from dialysis, in addition to be economically advantageous.

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