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Early experience with the ET Senior Program "Old For Old"; better to be number one?

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Abstract Eurotransplant offers a Senior Program to extend the donor pool for renal transplantation. The study comprised 14 patients of the ET Senior ("Old For Old") Program. Kidneys from five cadaveric donors were transplanted in pairs to ten recipients with a difference in cold ischemia time (CIT) of >4 h, and grouped according to CIT (group 1: patients that underwent transplantation first; group 2: patients that underwent transplantation second). CIT was shorter (5.5 ± 2.0 h vs. 11.7 ± 3.1 h, $P < 0.01$), and the first day diuresis was higher (287.4 ml/h vs. 134.8 ml/h, $P < 0.05$) in group 1 than in group 2. No patient in group 1 required dialysis, 3/5 patients in group 2. Rejection episodes occured more often in group 2 (5/5 vs. 3/5), and the hospital stay tended to be shorter in group 1 (33.0 days (27–43) vs. 54.2 days (27–112)). Our study confirms the positive effect of ultra-short CIT on early graft function in marginal donors, despite overall short CIT. The increase in delayed graft function (DGF) may lead to an extended hospital stay and dialysis requirements. Efforts to realize simultaneous transplantation in two recipients seem necessary to optimize results.

Keywords ET Senior Program · Cold ischemia time · Kidney transplantation

Abbreviations *AR* Acute rejection · *ATG* Antithymocyte globulin · *CIT* Cold ischemia time · *DGF* delayed graft function · *EGF* Early graft function · *ERSD* end stage renal disease · *ET* Eurotransplant

Introduction

In recent years, the number of renal transplantations has been stagnant in western Europe, despite annually increasing numbers of patients on the waiting list. In conjunction with the participating transplant programs, Eurotransplant (ET) initiated the ET Senior ("Old For Old") Program (ET newsletter, 151; Jan 4th 1999) to improve this unsatisfactory situation. This program was designed for non-immunized recipients of a first graft older than 65 years with end stage renal disease (ERSD), who otherwise would have limited opportunity to receive a suitable organ within an acceptable time. These patients are enrolled to receive kidneys from regional donors aged over 65 years, allocated merely by AB0-compatibility and negative cross match. The major advantages of this program are the reduction of cold ischemia time and overall increase of the donor pool. The feasibility of successful transplantation of kidneys from old ("marginal") donors has been demonstrated previously, as well as the crucial role of short cold ischemia time [5].

This program was introduced at our center in August 1999. Since then, 14 patients have undergone transplantation. From six cadaveric donors, twelve patients received in pairs an organ. Kidneys transplanted first,

i.e. kidneys with shorter CIT, appeared to be superior with regard to initial graft function and the rate of complications, as suggested in a previous paired study by Tandon et al. [10] in non-marginal donors. A positive effect of CIT as well as transplantation technique (double or single renal transplantation) on the graft outcome has already been demonstrated in "regular" and "marginal" donors [3, 5]. These effects were more pronounced after transplantation of marginal kidneys [3, 5]. The aim of the present report was to study the effect of sequential transplantation, i.e. transplantation of one kidney after the other within pairs of marginal kidneys, with regard to early outcome.

Patients and methods

All renal transplantations performed in the ET Senior Program at the University of Regensburg were included, regardless if either one or both kidneys from the same cadaveric donor were transplanted. Allocation of the donor kidney was performed according to blood type compatibility without HLA matching. All transplantations were performed by the surgical transplant team in our hospital, using standard surgical techniques. The kidneys were placed extraperitoneally in the left or right fossa iliaca and anastomosed according to operative standards. Post-operative immunosuppression is shown in Table 1. All patients received a standard triple immunosuppression therapy consisting of either tacrolimus or cyclosporin A, azathioprine or mycophenolate mofetil and prednisolone. Acute rejection (AR) episodes were diagnosed clinically and confirmed by biopsy in 6 of 9 cases. AR was treated with a steroid regimen of 250 mg prednisolone for 3 days, and, in cases of steroid resistance, by a switch of immunosuppression to tacrolimus and/or antithymocyte globulin (ATG).

10 patients who received in pairs a kidney from the same donor were evaluated. These patients were grouped according to their order of transplantation. Thus group 1, the first to undergo transplantation, has a significantly shorter cold ischemia time (CIT) than group 2, the second to undergo transplantation. An additional analysis included four patients, two of whom did not undergo transplantation in pairs, and two further patients who received kidneys in pairs and underwent transplantation simultaneously. They were included in the overall description. The decision on whom to choose first for transplantation was made according to clinical criteria (e.g. the need for pre-transplant dialysis) or, if both patients were equally ready for surgery, on the principle of "first come, first serve". Early graft function (EGF) was assessed by monitoring the first day diuresis and the fall of serum creatinine from pre-transplant levels to the end of the first week by extrapolating the daily levels [10]. Delayed graft function (DGF) was defined as the necessity of post-transplant dialysis [6]. Creatinine clearance was calculated according to the method by Cockcroft and Gault [1].

Statistical methods

Statistical analysis was performed with GraphPad Prism. Demographic data and diuresis were compared with Student's *t*-test. For calculation of differences in the incidence of posttransplant dialysis and acute rejection, Fisher's exact or chi-square test were used, and for comparing the decrease in serum creatinine concentration the daily levels from days 1–7 were extrapolated by linear regression, and slopes were compared with Student's t-test. Spearman rank correlations were calculated between hospitalization time and diuresis and cold ischemia time. *P*-values less than 0.05 (two-tailed) were considered as statistically significant, and results are presented as mean ± SEM.

Results

All patients who underwent transplantation in the ET Senior Program at the University Hospital of Regensburg were included in our study and analysed in their respective subgroups according to their individual mode of transplantation.

Patient groups receiving a kidney as first or second recipient were comparable with regard to age, donor age, mode and duration of dialysis, underlying disease, and HLA-match (Tables 1 and 2). Overall, more men underwent transplantation than women, and group 1 consisted of men only. Two patients were not ≥ 65, but > 60 years at the time of transplantation. ET offered these patients a kidney in the Senior Program for lack of suitable recipients on the standard waiting list, which would have lead to an unacceptable risk of prolonged cold ischemia time of the marginal organs. CIT in group 1 (5.5 ± 2.0 h) was by definition significantly shorter than in group 2 (11.7 ± 3.1 h; $P < 0.01$). Also, first day diuresis, an indicator for the primary function of the graft, was significantly higher ($P < 0.05$) in group 1, also when corrected for residual diuresis. Post-transplant dialysis was only necessary for patients in group 2. Furthermore, clinical and/or histological findings (6 of 8 patients) of acute rejection were observed more often in group 2 (3/5 vs. 5/5, n.s.). Rejection episodes could be managed with steroid pulse therapy and/or switch of cyclosporine A to tacrolimus in 7/8 cases. There was one case of steroid resistant graft rejection (patient 10), but this graft had not functioned adequately from the start and was explanted 5 months later because of chronic rejection. During follow up, two patients died with good graft function, one patient with concomitant cardiovascular disease from sudden cardiac death (patient 11), the other from gastrointestinal bleeding and sepsis (patient 1). Serum creatinine concentrations decreased with improving initial graft function (i.e. first day diuresis) in group 1. While pre-transplant serum creatinine concentrations were not significantly different in the two groups (7.7 ± 0.6 mg/dl vs. 8.4 ± 0.4 mg/dl; n.s.), serum creatinine concentrations decreased more rapidly in group 1 by day 7 (Fig. 1, $P < 0.001$). The average duration of hospital stay was markedly lower in group 1; however, the difference did not reach statistical significance. All patients in group 1 could leave the hospital earlier than those in group 2. In times of decreasing budgets and limited resources this fact proves to be of great importance. In the calculated Spearman correlation, hospitalization time correlated significantly with first day diuresis. (–0.53, $P < 0.05$).

Table 1 Detailed patient characteristics (*FK-506* tacrolimus, *CsA* cyclosporine A, *Aza* azathioprine, *MMF* mycophenolate mofetil, *P* prednisolone, *GN* glomerulonephritis)

Patient no.	Age (years)	Gender	Underlying disease	Donor age (years)	CIT	Mismatches	Initial immunosuppression	Duration and type of dialysis
1, Group 1	69	M	Unspecified GN	68	2 h 39 min	6	FK-506, Aza, P	6 years 2 months HD
2, Group 2	66	F	Analgesic nephropathy	68	7 h 27 min	3	FK-506, Aza, P	2 years 7 months HD
3, Group 1	69	M	Membranous GN	69	3 h 05 min	6	CsA[a], Aza, P	5 years 8 months HD
4, Group 2	68	M	Diabetic nephropathy	69	8 h 40 min	5	CsA[a], Aza, P	4 years 11 months HD
5, Group 1	64	M	ADPKD	76	3 h 33 min	2	FK-506, Aza, P	3 years 3 months HD
6, Group 2	66	M	Diabetic nephropathy	76	8 h 32 min	5	FK-506, Aza, P	1 year 6 months HD
7, Group 1	70	M	Unspecified GN	67	5 h 02 min	5	CsA, MMF, P	3 years 4 months HD
8, Group 2	68	M	Unspecified GN	67	10 h 00 min	5	FK-506, Aza, P	1 year 1 month HD
9, Group 1	61	M	Unspecified GN	75	13 h 06 min	4	FK-506, Aza, P	1 year 8 months HD
10, Group 2	66	F	Unspecified GN	75	24 h 00 min	6	FK-506, Aza, P	3 years 1 month HD
11, Simultaneously	71	M	Unspecified GN	81	11 h 50 min	4	FK-506, Aza, P	4 years 7 months HD
12, Simultaneously	66	F	Unspecified GN	81	12 h 25 min	2	FK-506, Aza, P	1 year 11 months HD
13, Not in pairs	69	M	Unspecified GN	70	21 h 50 min	0	CsA[a], Aza, P	4 years 8 months HD
14, Not in pairs	73	F	Unspecified GN	66	4 h 20 min	5	FK-506, MMF, P	1 year 5 months HD

[a]According to the rejection regimen these patients were switched to tacrolimus

Table 2 Demographic and transplantation-related data in the different groups. Statistical analysis was performed by Student's paired *t*-test or Fisher's exact test where appropriate

Parameter	Whole group ($n=14$)	Group 1, transplanted first ($n=5$)	Group 2, transplanted second ($n=5$)	*P* value, group 1 vs group 2
Gender (F/M)	4/10	0/5	2/3	0.18
Mean age (range) in years, patients	67.6 (61–73)	66.6 (61–70)	66.8 (66–68)	0.67
Mean age (range) in years, donors	71.5 (66–81)	71 (67–76)	71 (67–76)	–
CIT (h)	9.8 ± 1.8	5.5 ± 2.0	11.7 ± 3.1	0.006
Mean residual diuresis (range) in ml/day	535.7 (0–2000)	260.0 (0–800)	1000.0 (500–2000)	0.12
Mean diuresis (range), first day in ml/h	189.4 (0–523)	287.4 (72–523)	134.8 (5–350)	$P<0.05$
Mean diuresis (range) minus residual, (first day)	168.5 ml/h (0–505)	276.4 ml/h (44–505)	109.8 ml/h (5–267)	$P<0.05$
Posttransplant dialysis (yes/no)	4/10	0/5	3/2	0.17
Hospitalization time (range) in days	40.9 (21–112)	33.0 (27–43)	54.2 (27–112)	0.24
Mean number (range) of mismatches	4.1 (0–6)	4.6 (2–6)	4.8 (3–6)	0.86
Rejection (yes/no)	9/5	3/2	5/0	0.44
Serum creatinine (mg/dl)/creatinine clearance (ml/min) mean ± SD				
Day 7	3.85 ± 0.70/29.3 ± 4.6	2.77 ± 0.53/34.8 ± 6.8	5.00 ± 1.58/24.1 ± 8.8	0.11
Day 14	3.33 ± 0.55/31.3 ± 5.1	2.20 ± 0.25/42.5 ± 7.0	4.62 ± 1.10/21.5 ± 6.3	0.10
Day 21	3.15 ± 0.48/35.5 ± 5.5	2.48 ± 0.51/43.4 ± 8.1	4.79 ± 1.00/24.0 ± 8.9	0.11
Day 28	3.08 ± 0.48/–	2.66 ± 0.65/–	4.17 ± 1.06/–	0.20
Day 90	2.17 ± 0.30/– ($n=13$)	2.07 ± 0.38/– ($n=4$)	2.37 ± 0.74/– ($n=5$)	0.61

Discussion

In this paired-case-control design (each patient had his own control in the other patient who received the contralateral kidney) we were able to study the effect of CIT on outcome after renal transplantation from marginal donors in the ET Senior Program ("Old For Old"). Since renal transplantations are often performed outside

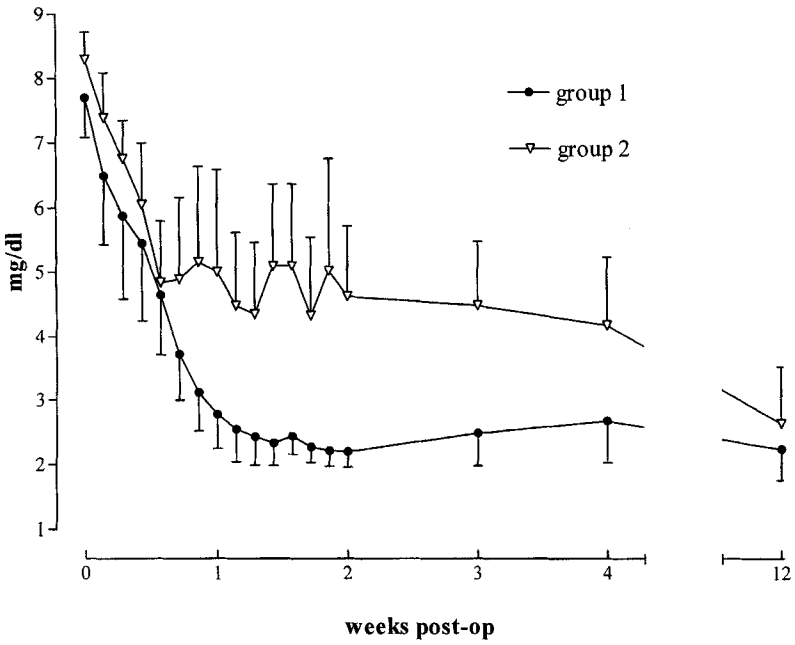

Fig. 1 Decrease in post-operative serum creatinine concentrations

regular working hours, operating theatre and staff capacities are limited. Consecutive transplantation of two kidneys from one donor was therefore unavoidable in the majority of cases, but was thought to be of no severe consequence, providing total CIT was held well below 24 h [4].

Previous studies have demonstrated a marked impact of CIT on early graft function, especially with regard to extremely long preservation times of 37–48 h [8]. However, these studies compared regular organs from normal donors. Tandon et al. [10] demonstrated the important factor of the CIT (14.1 ± 5.7 h vs. 19.2 ± 6.9 h) for initial graft function in kidney transplantation, when comparing two recipients who each received an organ from a single cadaveric donor, whereas Gokhan et al. [2] (21.9 ± 9.2 h vs. 25.7 ± 10.2 h) could not confirm this. The major difference between these observations and our series is the use of marginal donors. The major aim of our study was to reduce CIT as much as possible. Gokhan et al. [2] reported a CIT for the first transplanted organ of 21.9 h, whereas in our study we were able to reduce CIT to an average of 5.5 h for the first, and 11.7 h for the second kidney transplanted. This CIT compares favourably with CITs achieved by most other transplantation centers. Very recently Schlieper et al. [9] reported the results of 10 patients transplanted in the ET Senior Program. They could also reduce the CIT to an average of 13.3h ± 5.7, 5 h less than in "regular" renal transplantation. They found a high incidence of acute rejection episodes (7 of 10 patients), similar to our results (9 of 14 patients), but duration of hospital stay was longer, and delayed graft function more frequent 9 of 10 vs. 4 of 14 patients in their observation group. These data from Schlieper et al. [9] support our conclusion to reduce CIT in this special form of renal transplantation.

Furthermore, despite good overall CIT, early graft function and reduction of serum creatinine proved to be superior in group 1 (Fig. 1). Our data underline the importance of the non-immunological factor CIT, in the special context of the ET Senior Program utilising marginal donors, i.e. patients who were "number one" in the order of transplantation seem to have a better outcome. Short CIT has already been suggested to significantly influence early graft function, long term graft survival, and the mortality rate [7]. As mentioned above, good early graft function correlates negatively with duration of hospital stay, a fact which has also been demonstrated by Tandon et al. [10]. This potential economic benefit (21 days in hospital ~8400 EUR) may become of increasing interest in the light of limited financial resources.

Thus, a seemingly irrelevant average delay of 5–6 h leads to a significant drop in first day diuresis and early graft function, despite overall short CIT. Therefore it appears to be advantageous to be the first of a pair of patients to undergo transplantation of marginal kidneys. Our ongoing interest will be to further improve the coordination within all members of the transplant team, in order to limit cold ischemia time by parallel transplantation, as recently performed at our center with virtually identical results.

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