Transplant International ISSN 0934-0874

ORIGINAL ARTICLE

Long-term follow-up of double kidney transplantation using a score for evaluation of marginal donors*

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Keywords
double kidney transplantation, functional weight, glomerulosclerosis, marginal donor.

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*This paper was presented at the 11th ESOT Congress in Venice, September 20–24, 2003.

Received: 10 October 2003
Revised: 7 June 2004
Accepted: 1 November 2004

doi:10.1111/j.1432-2277.2004.00068.x

Summary

To face the problem of organ shortage, marginal grafts from 36 donors which had been refused for single transplantation were used for double-kidney transplantation (D-KTX). The residual kidney function was evaluated by the Muenster double kidney score. In a 5-year period kidneys from 57 marginal donors were transferred to our center. According to the Muenster double kidney score, the kidneys were distributed to single, double or refusal of transplantation. Sixteen male and 20 female donors were used for D-KTX (70±9.3 years, range 53–86). Thirty-six recipients (23 male, 13 female; 60.5±6.9 years) were double-grafted within a mean cold ischemic time of 19.3±3.4 h. Immunosuppression varied according to human leukocyte antigen (HLA)-mismatch. Graft and patient survival was observed up to 5 years. Initial graft function rate was 69%. Two recipients had a primary nonfunction (5.5%) and nine recipients suffered from delayed graft function (DGF; 25%). One-, 2-, 3-year creatinine values were 1.6 ± 0.5, 1.9 ± 0.6 and 2.2 ± 0.7 mg/dl, respectively. One-, 2-, 3-, 4- and 5-year function rate was 93.7%, 93.5%, 81.8%, 76.4% and 55%, respectively ($n = 32$, 31, 22, 17 and 9). Acute rejection rate was 19%. 4 grafts were lost to chronic rejection (months 22, 25, 28, 48). Six (16%) died in long-term follow-up because of pneumonia ($n = 2$), carcinoma of the lung ($n = 1$), cardial complications ($n = 2$) and multiorgan failure ($n = 1$). D-KTX is a safe way to face the problem of organ shortage. However, a score for preoperative evaluation of marginal kidneys for single, dual or refusal of transplantation is essential.

Introduction

Organ shortage has led to different compensation strategies. On the one hand, living donation from related and nonrelated donors is a safe option which is offered in nearly any transplant center. For the patient on hemodialysis this is a shortcut to better life quality, medically as well as socially. Long-term function of living donated grafts is excellent and therefore gives the recipient a long lasting possibility to avoid dialysis with its negative side effects concerning cardio-vascular complications and other problems.

As a living donor is not available for all patients on the waiting list, the use of renal transplants from marginal donors has become more common to shorten waiting time. Different procedures in the use of these kidneys have been tested [1–3]. In our center we evaluated residual kidney function by the Muenster double kidney score. Using the kidney weight and degree of glomerulosclerosis the kidneys were distributed to single, double or refusal

of transplantation. In this study we report about the results and experiences with the 'two-in-one' double-kidney transplantation (D-KTX) which was performed using organs from 36 marginal donors which had not been accepted for single transplantation in the Eurotransplant community.

Patients and methods

From 1996 to 2003 kidneys from 57 marginal donors were transferred to the Muenster transplant center, which had not been accepted for transplantation in other centers in the Eurotransplant community.

The reasons for rejection of these kidneys for single transplantation in other centers were various. In some cases, especially in the early period of our program, it was age only which stopped others from transplantation, in other cases it was the rising creatinine before harvesting the organs. As long as an internationally accepted definition of 'marginal donor' does not exist, donors are defined as 'marginal donors' whenever kidneys are refused by other centers because of supposed impaired kidney function as a result of donor age, creatinine, hypotensive periods prior to harvest and others.

According to a special score, these kidneys were distributed to single, double-kidney or refusal of transplantation. At the beginning of the program this score focused on donor age, degree of glomerulosclerosis, kidney weight and donor creatinine. Later on we recognized that the oldest grafts did not necessarily have severe glomerulosclerosis and vice versa, as some kidneys with mild degree of glomerulosclerosis were distributed to D-KTX because of high age and increased donor creatinine. So we varied our score and reduced it to 'functional weight' (FW) starting with patient 26. This score was based on histological specimen which detected the degree of glomerulosclerosis in the grafts.

All biopsies were wegde frozen-section biopsies. As far as the explantation was performed by our own team, biopsies were taken at time of retrieval to be analyzed by one pathologist. In case of external explantation without the possibility of frozen-section biopsies, they were taken at our center as soon as grafts were at hand; otherwise external frozen sections were accepted if wedge biopsies were performed. The quantification of the grade of glomerulosclerosis was determined by a simple morphometric analysis asking for a minimum of 15 glomeruli present in the wedge section. If this was not achieved, biopsies were not repeated because cold ischemic time would have been more than acceptably prolonged. In these cases the worst case of glomerulosclerosis was presumed (e.g. two of eight glomerula showed sclerosis means 25% sclerosis).

The percentage of glomerulosclerosis was then subtracted from the weight of the graft so that a new FW was calculated which represents the mass of intact glomerula {FW = weight of kidney × [100 − degree of glomerulosclerosis (%)/100]}. The cut-off point using the new score for evaluation was 150 g of FW for our center. In case of FW of >150 g a single transplantation was carried out. If a single kidney had a FW of <150 g, a D-KTX was performed using both kidneys from one donor to reach the total of 150 g FW. If both kidneys weighed <150 g FW because of severe glomerulosclerosis, they were rejected for transplantation.

Kidneys that were distributed to double transplantation were restricted to recipients older than 60 years if available in acceptable time with an acceptable mismatch. Each of the recipients was informed about the strategy to accept marginal donor for double kidney transplantation that had been rejected for single transplantation. The recipients were fully informed about the character of the kidneys and their special risk of primary nonfunction or diminished long-term function. Graft survival time was based on time with no need for dialysis. As usual, graft survival was censored to death with functioning grafts.

The immunosuppressive regimen varied according to HLA mismatch, number of transplantation (first, second or third) and initial graft function. Later on (starting with patient 24) immunosuppression was altered because of the high complication rate with infections: the chimeric anti-interleukin-2-receptor antibody, basiliximab, was given twice with 20 mg i.v. on day 0 and 4. According to these guidelines, 31% received a combination therapy with CyA/IL2-receptor-Ab/prednisolone, 28% received CyA/MMF/prednisolone; another 28% were on combination of Tacrolimus (FK506)/MMF/prednisolone and 8% received dual therapy with CyA/prednisolone or Tacrolimus (FK506)/prednisolone (5%). Trough level for Tacrolimus (FK506) was aimed at 8 ng/ml, for CyA at 100 ng/ml. Prednisolone was tapered down from 1 g to 20 mg/day on day 7 after transplantation. MMF was given twice a day at a dosage of 1 g.

Doppler-ultrasound was carried out on a daily basis in the first week after transplantation. In addition, 26 of 36 D-KTX recipients underwent a scintigrafic evaluation of the transplants to find out if one or the other kidney takes more of the function.

Results

Distribution of kidneys

Sixteen male and 20 female donors were used for D-KTX. Their mean age was 70 ± 9.3 years (range 53–86). These kidneys were allocated to 36 recipients (23 male, 13 female) with mean age of 60.5 ± 6.9 years who were

double-grafted within a mean cold ischemic time of 19.3 ± 3.4 h (range 8–26) (Table 1). The mean FW that was calculated for all grafts being transplanted as double kidney transplantation measured 141.3 ± 35 g. In 29 cases the transplantation was performed on one side of the recipient and seven patients were grafted with one kidney on each iliac vessel because of severe arteriosclerosis which made a unilateral transplantation impossible. Mean HLA mismatch was 1,1 (A), 1,38 (B) and 0,88 (DR). 33 patients were transplanted for the first time, two patients received their second organ, one patient was grafted for the third time.

A group of 10 recipients that were distributed to single transplantation at our center with a FW >150 g was used as a reference group for the double graft recipients. There was no significant difference between the two groups concerning donor age (D-KTX: 70 ± 9.3 vs. single KTX: 71 ± 3.0) or cold ischemic time (D-KTX: 19.3 ± 3.4 vs. KTX: 18.0 ± 4.0).

Follow-up

Graft function

After a mean follow-up of 39.5 months (range 4–67), 24 of 36 (63%) D-K-transplants show function. The 1-, 2-, 3-, 4- and 5-year graft survival rate is 93.7%, 93.5%, 81.8%, 76.4% and 55%, respectively ($n = 32, 31, 22, 17, 9$; Fig. 1). Creatinine values after 12, 24 and 36 months

Table 1. 36 Double-kidney transplanted patients. Operative details and early postoperative events (CIT: cold ischemia time).

No.	Recipient age	Donor age	TX-procedure	CIT	Early postoperative event
1	50	75	Unilateral	19	Delayed graft function
2	55	68	Unilateral	21	Delayed graft function
3	56	69	Unilateral	25	Primary function
4	49	74	Bilateral	18	Primary function
5	55	70	Unilateral	20	Delayed graft function
6	57	69	Unilateral	26	Delayed graft function
7	53	65	Unilateral	20	Primary function
8	54	70	Unilateral	20	Primary function
9	51	73	Unilateral	20	Primary function
10	59	71	Bilateral	19	Primary function
11	64	72	Unilateral	19	Primary function
12	68	84	Unilateral	19	Primary function
13	62	73	Bilateral	23	One kidney lost (arterial thrombosis left kidney); Delayed graft function
14	58	65	Unilateral	21	Primary function
15	63	68	Unilateral	21	Primary function
16	58	74	Unilateral	19	Delayed graft function
17	50	72	Bilateral	18	Delayed graft function
18	58	74	Unilateral	24	Primary function
19	59	79	Unilateral	20	Primary function
20	68	68	Unilateral	23	One kidney lost, (septic infarction)
21	68	70	Unilateral	16	Primary function
22	71	65	Unilateral	20	Primary function
23	48	53	Unilateral	22	Primary function
24	69	78	Unilateral	20	Primary function
25	66	69	Unilateral	21	Delayed graft function
26	68	76	Unilateral	19	Primary function
27	60	86	Unilateral	21	Primary function
28	70	64	Bilateral	24	Primary function
29	60	75	Unilateral	18	Primary function
30	68	76	Bilateral	18	Delayed graft function
31	66	77	Unilateral	18	Primary function
32	66	72	Unilateral	18	Primary nonfunction (thrombosis of both kidneys)
33	66	65	Bilateral	15	Primary function
34	51	65	Unilateral	11	Primary nonfunction
35	68	72	Unilateral	19	Primary function
36	69	85	Unilateral	8	Primary function

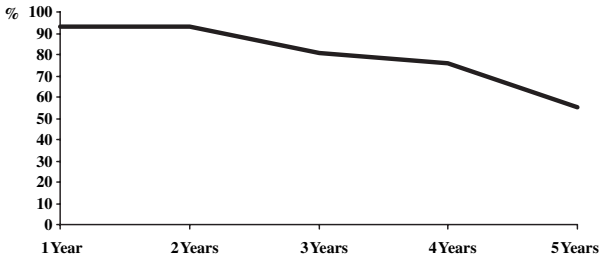

Figure 1 Graft survival following double kidney transplantation from marginal donor.

after D-KTX proved good function of the grafts in the first 3 years (12 month: 1.6 ± 0.5 mg; 24 months: 1.9 ± 0.6 mg; 36 months: 2.2 ± 0.7 mg). Regarding creatinine at 12 months post-transplant, recipients of D-KTX turned out to show even better values than recipients of a single 'marginal' KTX (2.3 ± 0.7 mg/dl in single-KTX versus 1.6 ± 0.5 in D-KTX; $P < 0.05$). However, this could not be proved for the long-term run so far.

The rate of primary nonfunction was 5.5% ($n = 2$), a delayed graft function (DGF) was seen in nine patients (25%). Four grafts were lost because of chronic rejection 22, 25, 28, and 48 months after double transplantation. One pair of cadaveric kidneys was lost because of venous thrombosis in early postoperative course (day 5) which was added up as one of two above mentioned primary nonfunctions.

One kidney in a double grafted 62-year-old woman was lost 4 days after transplantation because of arterial and venous thrombosis of the left kidney. Another 68-year-old recipient lost one graft 7 months post-transplant because of septicemic infarction. The first mentioned patients showed a reasonable graft function with serum creatinine value of 2.5 mg/dl (month 36); the second patient had a serum creatinine of 2.3 mg/dl (month 22).

Biopsy-proven acute rejection episodes were seen in 19% ($n = 7$) of the double grafted recipients. Three of theses cases turned out to be corticoid resistent and were successfully treated with antibodies (ATG).

Routine doppler-ultasound in early postoperative period revealed good perfusion of both kidneys except for the above mentioned cases of early graft loss because of thrombosis of either one or both kidneys which was detected by this method. Scintigrafic evaluation of 26 D-KTX recipients could not detect a difference between function of the two kidneys, either in unilateral or in bilateral transplant procedure (Fig. 2).

Patient survival

Six (16%) of 36 D-KTX patients died in the long-term follow-up because of pneumonia ($n = 2$, 4 and 25 months post-D-KTX), carcinoma of the lung ($n = 1$, month 27), cardial complications ($n = 2$, month 48, 31) and multiorgan failure of unknown origin ($n = 1$, month 3). CMV infection was detected in 11% of the recipients.

Discussion

The demonstrated results underline that D-KTX is a safe way to face the problem of organ shortage by using marginal donors which are not acceptable for single transplantation even with short ischemic time [4,5]. Grafts that would have been rejected for transplantation were used to perform transplantation in 36 recipients long-term waiting for a conventional transplantation.

As long as an internationally accepted definition of 'marginal donor' does not exist, personal experience of

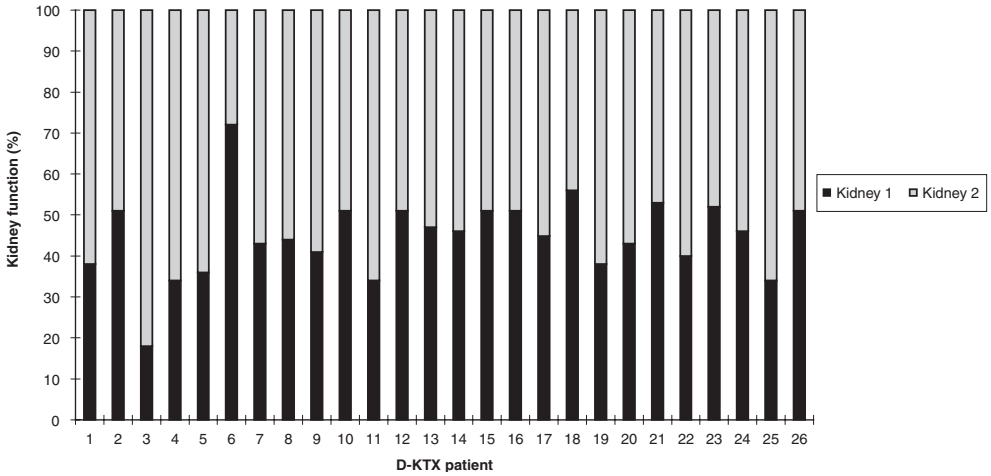

Figure 2 Scintigrafic evaluation of kidney function 3 months after double kidney transplantation: both kidneys show function in any of the recipients. Bilateral transplant procedure was performed in recipient 4,10, 13, 17, 28, 30, 33.

the transplant center still plays an important role in acceptance of these donor organs. However, different risk factors are known which should be reconsidered when developing a score for evaluation of these kidneys.

First of all, donor age is a well-known risk factor in cadaveric kidney transplantation [6–8]. So whenever evaluating a marginal donor for transplantation it is necessary to focus on donor age.

Nevertheless, nephron mass is known as a major determinant of long-term renal allograft outcome [9] so the degree of glomerulosclerosis of the graft should also play an important role in the determents of long-term outcome after renal transplantation in using 'marginal' as well as 'conventional' and even living donated grafts. According to the hyperfiltration theory of Brenner *et al.* [10], in marginal donor kidneys there is a critical mass of functionally capable nephrons, and if this drops below a certain level, it will lead to further loss of nephrons as a consequence of a vicious circle. The aim of double kidney transplantation was therefore to make a sufficient number of functionally capable nephrons available by transplanting two kidneys so as to ensure adequate kidney function in the long-term.

Therefore the Muenster double kidney score which aims to determine the number of functionally capable nephrons is useful to detect whether a marginal cadaveric kidney should be refused for transplantation or whether it is suitable for single or dual kidney transplantation. In the beginning of our program, soon after Brenner's hyperfiltration theory became evident [10], we developed a score using donor age, donor creatinine, weight of kidneys and degree of glomerulosclerosis as the basis for evaluation. Later on we recognized that high donor age may mislead the decision of distribution of kidneys to single, dual or refusal of transplantation because of the fact that donor age does not necessarily correlate with the number of functionally capable nephrons. Consequently our score was modified to the 'FW' which is based on degree of functionally capable nephrons only.

On the one hand, initial nonfunction of grafts and on-going function in spite of loss of one of the double transplants may indicate that the score still has to be expanded by more details of the donor and maybe of the recipient as well. On the other, scintigrafic evaluation could demonstrate that functional nephron supply can effectively be increased by double kidney transplantation whenever conventional single transplantation may not be possible because of various donor dependent reasons.

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