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Kidney procurement from non-heartbeating donors: transplantation results

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Abstract. To overcome the shortage of kidneyes (kdn's) available for transplantation we reactivated kdn procurement from non-heartbeating donors (NON-HBD). In this study, we reviewed our results with 34 kdn's from NON-HBD, transplanted between 1985 and 1991, and compared these with 34 control kdn's procured from heartbeating donors (HBD) matched for age, sex, primary graft or retransplant and transplant year. There was no difference in cold ischemia time, preservation solutions used, duration and type of preoperative dialysis, number of HLA mismatches and serum antibody levels between the two groups. The only significant findings were a lower diuresis in the last hour in the donors in the NON-HBD group, and a significantly higher serum creatinine level compared to the HBD group. The 1-year patient and graft survival rates were 89.4% and 84.9% for the HBD group, and 78% and 76.1% for the NON-HBD group respectively. There was need for dialysis support in the first post-transplant week in 10 out of 34 (29%) recipients in the HBD and 17 out of 34 (50%) recipients in the NON-HBD group. Primary non-function was observed in 1 of 34 (3%) recipients in the HBD group versus 3 of 34 (9%) in the NON-HBD group. None of the differences were statistically significant. There was also no difference in average serum creatinine levels at days 1, 3, and 7, at 1 month and at 1 year between the HBD and NON-HBD groups. In the NON-HBD group 6 of 34 kdn's (18%), 5 of which were retransplants, showed vascular rejection, 5 of them associated with haemolytic uremic syndrome (thrombotic microangiopathy); 2 of these 6 kdn's recovered, and 4 failed (2 with primary non-function). This important observation needs to be investigated further. The results is this study showed, however, that good short- and long-term results can be achieved with kdn's from NON-HBD. We concluded that organ procurement from NON-HBD is an adequate approach to an important cadaver donor source that in general is not effeciently used, but could significantly increase the number of kdn grafts in most transplant programs.

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Key words: Non-heartbeating donor – Vascular rejection – Hemolytic uremic syndrome

The shortage of donor kidneys [kdn] is the main cause for increasing waiting lists among patients awaiting a transplant and obliges to an efficient use of all donor sources. We have performed kdn retrieval from non-heartbeating donors [NON-HBD] in the recent past. In this study we reviewed our results with kdn's from NON-HBD and compared them with those from heartbeating donors [HBD].

Patients and methods

Study design

Between January 1985 and September 1991, 482 kdn were transplanted at our institution. During this period we procured 38 kidneys from 19 NON-HBD (14 kdn between 1985 and 1989, 10 kdn in 1990, and 14 kdn between January and September 1991); 34 were grafted at our clinic (4 elsewhere) and taken for retrospective analysis (NON-HBD group). For comparison we selected an equal number of kdn transplants who satisfied the following criteria: procurement only from HBD, recipients of the same sex, same age (same decade), same number of transplant (primary or retransplant) and same period (±6 months) of transplantation (HBD group).

Donor demographics

NON-HBD group. Donors suitable for postmortem kdn procurement are emergency patients dying from circulatory arrest as a consequence of either intractable hemorrhagic, – and rarely cardiogenic, shock, or of cardiovascular dysregulation caused by cerebral fatalities (or a combination in both). Most often these are trauma patients with fatal head injuries alone or combined with multitrauma, less frequently, they are patients suffering from non-traumatic intracerebral bleeding or ischemia and very seldom patients with heart disease. Some of these patients die in the ambulance or emergency room, others develop sudden circulatory instability in the intensive care unit and die in circulatory arrest. Since many hospitals require two electroencephalograms 24 h apart in order to use the patient as a HBD, most of these potential donors would be lost

for organ procurement. However, nephrectomy can be performed after cardiac arrest. Whenever possible we brought these patients to the operating room before circulatory arrest had been established and procurement of the kdns was started immediately.

Of the 19 NON-HBD included in our study, 16 died from fatal head injury, 2 from ruptured cerebrovascular aneurysms and 1 from asphyxia. Of the 38 kdn's procured, 4 were shipped to other transplant centers, and 34 were transplanted in our institution and included in this study.

HBD group. Of the 34 donors in this group, 21 died from head injury, 6 from spontaneous cerebrovascular bleeding, 3 from cerebrovascular insult, 3 from anoxia and 1 from meningitis. All fullfilled the criteria for brain death and single or multiple organ procurement was performed under heartbeating conditions.

Table 1 gives a summary and comparison of other relevant donor data for both groups, i.e. donor age, need for catecholamines, diuresis during the last hour, serum creatinine level, presevation medium and cold ischemia time. Statistically relevant differences between the two donor groups were found for the last hour's diuresis which was significantly lower in the NON-HBD and for the serum creatinine levels which were significantly higher in the NON-HBD group. No significant differences were found for all other paramenters. Precise duration of warm ischemia time was not determined in most NON-HBD, because the exact moment when blood circulation ceased was not definable. Therefore, these data are not given for either group.

Donor operation

NON-HBD group. Heparin (20000 units) was given intravenously before cardiac arrest was established. A midline incision from the xiphoid to the pubis was performed followed by an incision of the posterior parietal peritoneum along the right colon. The right colon and the small bowel were mobilized and retracted superiorly and to the left. The distal vena cava and aorta were freed and the latter cannulated just above the bifurcation. The celiac axis, superior and inferior mesenteric arteries and inferior mesenteric vein were only ligated if their exposure was not time consuming. The proximal aorta was then isolated below the diaphragm, cross clamped and an in situ aortic flush was immediately initiated using either EuroCollins (EC) or University of Wisconsin (UW) solution. An incision in the distal vena cava allowed egress of cooling fluid. Care was taken that operating time to the beginning of the hypothermic flush was no more than 10 min. The kdn's and ureters were then mobilized. We did not usually carry out the en bloc removal of the kdn's but preferred to identify and dissect the renal vessels in situ. The aorta and vena cava were incised longitudinally and patches of the aorta and vena cava were excised for the renal vessels. The kdn's were then removed and again flushed on the backtable. We have recently described this technique elsewhere [1].

HBD group. The procurement technique in HBD for singe or multiple organ procurement has been described by others [2] and also by us [3] and remains unchanged.

Recipient demographics

NON-HBD group. The 34 recipients all suffered from end-stage renal disease caused by glomerulonephritis in 17, polycystic kdn disease in 4, chronic pyelonephritis in 4, diabetic nephropathy in 3, Alport's syndrome in 2 and other chronic kdn affections in 4 patients.

HBD group. Of these 34 selected kdn transplant recipients, 12 suffered from glomerulonephritis, 10 from polycystic kdn disease, 3 from chronic pyelonephritis, 2 from Alport' syndrome and 7 from other chronic renal diseases.

Table 2 gives a summary and comparison of other relevant recipient data and pretransplant risk factors for both groups, such as recipient age, sex, primary graft or retransplant, dialysis time and type hemodialysis or continuous ambulatory peritoneal dialysis, number of HLA-A, -B, -DR mismatches and sensitization (highest preoperative percentage of antibodies). None of these data showed a statistically significant difference between the two recipient groups.

Postoperative treatment

For the HBD group (and for the 9 kdn in the NON-HBD group transplanted before 1986) our standard triple immunosuppressive therapy was used: prednisone (1 mg/kg per day tapered to 0 at 6 month), azathioprine (1 mg/kg per day, continuously) and cyclosporine 5 mg/kg per day intravenously for the first days and thereafter orally in doses depending on serum trough levels (desired range: 200–400 ng/ml). For the NON-HBD group, the prednisone and azathioprine regimen was identical but, in 1986, initial cyclosporine was replaced by the intravenous administration of antithymocyte globulin (ATG 3 mg/kg per day) until serum creatinine levels reached a normal range, but maximally for 14 days. Oral cyclosporine therapy was started in equal doses as in the HBD-group, overlapping about the last 2 days of ATG administration. In all other respects (thromboembolic and infection prophylaxis, monitoring of organ function, and so forth) both groups had the same postoperative mangement.

Table 1. Donor demographics and kidneys. Donor and graft characteristics such as need for catecholamines and type of preservation solutions used are expressed as frequencies, data such as age, diuresis during the last hour, serum creatinine level and cold ischemia time are given as average ± standarddeviation

	HBD	NON-HBD	
Donors *(n)*	34	19	
Age years	31.1 ± 14.4	33.9 ± 12.5	P = ns
Use of catecholamines	27 (79%)	16 (84%)	P = ns
Diuresis last hour ml/h	317.3 ± 468.2	100 ± 103.3	$P < 0.05$
Serum creatinine µmol/l	87.9 ± 20.3	133 ± 62	$P < 0.05$
Preservation UW/EC	14/20	10/9	P = ns
Cold ischemia time h	15.7 ± 7.4	17.3 ± 5.9	P = ns

UW, University of Wisconsin organ preservation solution; EC, Euro-Collins organ preservation solution

Table 2. Recipient demographics. Relevant recipient characteristics such as distribution of sex, type of preoperative dialysis and number of transplant (primary graft or retransplant) are expressed as frequencies; other pretransplant risk factors such as age, duration of pretransplant dialysis, number of HLA-A, -B, -DR mismatches and sensitization (maximal preoperative percentage of antibodies) are expressed as average ± standard deviation

	HBD	NON-HBD	
n	34	34	
Age years	46.2 ± 12.4	45.7 ± 13	P = ns
Sex f/m	13/21	13/21	P = ns
Primary graft/retransplant	27/7	26/8	P = ns
Dialysis type HD/CAPD	29/5	25/9	P = ns
Duration of dialysis month	51 ± 45	52 ± 45	P = ns
HLA mismatches A	1.2 ± 0.5	1.1 ± 0.6	P = ns
B	1.3 ± 0.6	1.3 ± 0.5	P = ns
DR	0.6 ± 0.5	0.9 ± 0.5	P = ns
Maximal preop antibody levels %	25.2 ± 29.1	25.6 ± 27.1	P = ns

HD, Hemodialysis; CAPD, continuous ambulatory peritoneal dialysis

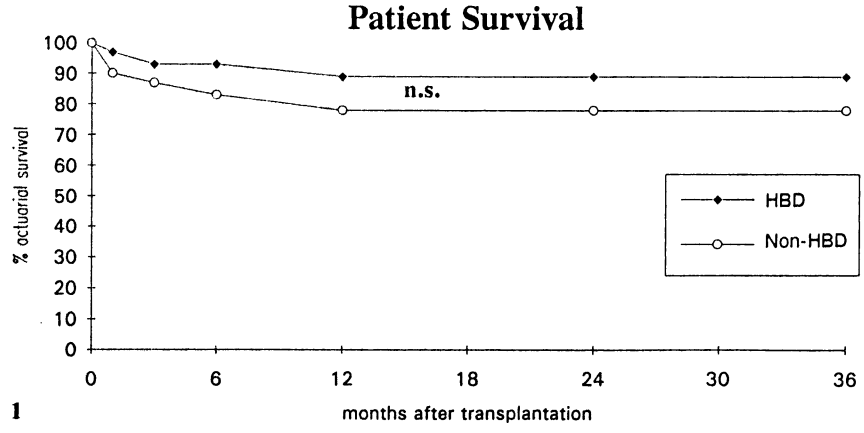

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Fig. 1. Patient survival rates following kidney allotransplantation according to the origin of the grafts: kidneys from heartbeating donors [HBD] or non-heartbeating donors [NON-HBD]

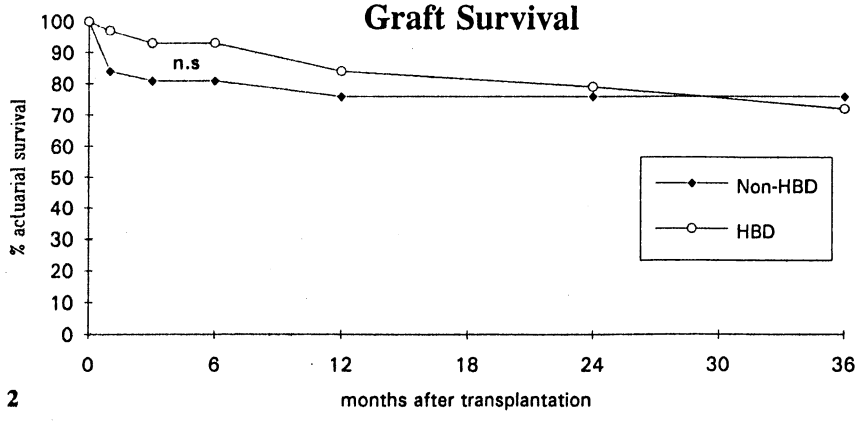

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Fig. 2. Renal graft functional survival rates for kidneys from heartbeating donors [HBD] and from non-heartbeating donors [NON-HBD]

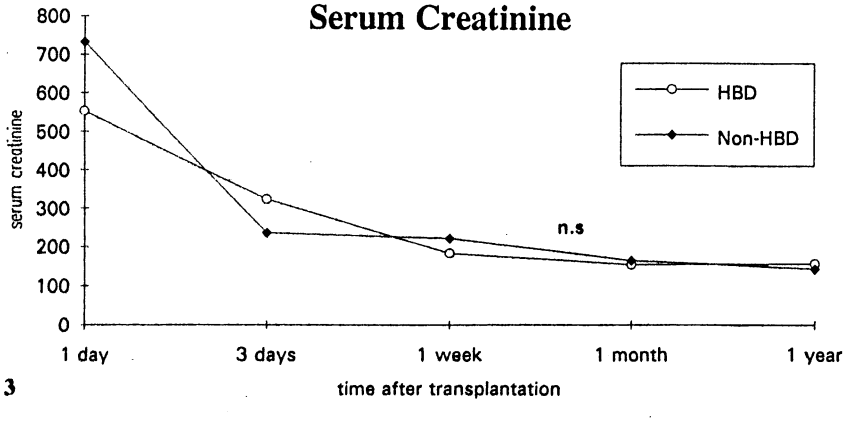

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Fig. 3. Course of posttransplant serum creatinine levels in the early and late postoperative period (day 1 to 1 year) for kidneys from heartbeating donors [HBD] and from non-heartbeating donors [NON-HBD]. For days 1, 3 and 7, only creatinine values from patients that were not on dialysis during this time were taken

Statistics

Patient and graft survival rates were calculated by an actuarial method (Cutler-Ederer) on September 30, 1991, giving a minimum follow up of 1 month and a maximum of 77 months. Statistical significance (P-value < 0.05) was determined by the Student's t-test for comparison of means and the Chi-square test for comparison of proportions.

Results

The 1-year patient survival rate was 89.4% for the HBD group, and 78% for the NON-HBD group. The 1-year kdn transplant survival rate was 84.9% for the HBD group, and 76.1% for the NON-HBD group. Patient and graft outcome for both groups are shown in Table 3 and depicted in Figs. 1 and 2. During the first posttransplant week 10 of 34 (29%) recipients in the HBD group and 17 of 34 (50%) recipients in the NON-HBD group needed dialysis support; diagnosis of acute tubular necrosis was assumed if clinical signs of acute rejection were absent and technical reasons were precluded. There was one case of primary non-function in the HBD group (3%) and three cases in the NON-HBD group (9%). The course of the serum creatinine levels in the early and late postoperative period for both groups is listed in Table 3 and depicted in Fig. 3. The comparison of all data showed no statistically significant differences between the two groups.

Major technical complications that needed surgical repair were four ureteric obstructions in the NON-HBD

Table 3. Results. Results such as incidence of temporary posttransplant dialysis support and occurrence of primary non-function are expressed as frequencies; postoperative serum creatinine levels are given as average ± standard deviation and patient and graft survival in percentages as calculated by actuarial method

	HBD	NON-HBD	
Temporary postoperative dialysis	10 (29%)	17 (50%)	P = ns
Primary non-function	1 (3%)	3 (9%)	P = ns
Creatinine μmol/l at 1 week	185 ± 113	223 ± 141	P = ns
Creatinine μmol/l at 1 month	154 ± 99.7	165 ± 101	P = ns
Creatinine μmol/l at 1 year	152 ± 92.5	147 ± 82.2	P = ns
1 year patient survival	89.4%	78%	P = ns
1 year graft survival	84.9%	76.1%	P = ns

group and three in the HBD group. There was one case of lymphocele in each group that needed surgical intervention.

Causes of graft failure or death

NON-HBD group. Of 34 transplanted kidneys in this group, 3 showed primary non-function; all 3 were retransplants and histological examination demonstrated acute vascular rejection; in two cases this was associated with haemolytic uremic syndrome. The same phenomenon (vascular rejection + haemolytic uremic syndrome) was observed in three more NON-HBD kidneys, two of which were retransplants; all had primary function, one graft failed at day 12, the other two recovered. Thus, 6 out of 34 kdn's (18%) in the NON-HBD group, 5 of which were retransplants, showed vascular rejection, 5 of them associated with haemolytic uremic syndrome (thrombotic microangiopathy); 2 of these 6 kdn's recovered, and 4 were lost (2 with primary non-function). One more graft failed from chronic rejection at 74 months. Two patients died with functioning grafts at 1 week and at 11 months from myocardial infarction and pneumonia respectively.

HBD group. Of 34 transplanted kidneys in this group, 1 showed primary non-function for unknown reasons. Three other grafts failed, one at 11 months due to recurrence of the original disease in the transplant (sclerosing glomerulonephritis), one at 19 months from chronic rejection and one at 31 months from undetermined reasons. Two patients in this group died with functioning grafts at 3 and 11 months from myocardial infarction and pneumonia respectively.

Discussion

To overcome the shortage of kdn's available for transplantation, we, along with other groups [4, 5], reactivated the concept of kdn retrieval from NON-HBD. However, at the beginning of this series we observed an increased incidence in the need for dialysis support during the first posttransplant week. Since it is known that delayed renal graft function due to acute tubular necrosis from preservation damage has a major imapct on the 1- and 5-year kdn graft survival [6], we tried some specific measures to improve the safety and success of this procedure.

For fear of increased risk of cyclosporine toxicity in kdn's from NON-HBD with inevitably prolonged warm ischemia time, we replaced the initial postoperative cyclosporine administration by ATG until serum creatinine levels reached a normal range (maximally 14 days). Since this modification in 1986, the need for temporary postoperative dialysis of kdn's from NON-HBD has been reduced from 89% (8/9) to 36% (9/25). However 18 of the 25 kdn with the new the immunosuppressive regimen were also preserved with UW solution, introduced to our program since 1989. It is not possible, in this study, to differentiate the impact of the two factors, but the clear improvement in results suggested that both measures are advantageous for kdn's from NON-HBD. Despite the potential benefit of UW, we intend to keep cold ischemia time for kdn's from NON-HBD below 24 h because the degree of preliminary damage from the uncertain duration of warm ischemia and from the administration of catecholamines is difficult to assess and further risks should be avoided. Provided that these precautions are respected, catecholamine administration (if not given over a prolonged period, and in exessive doses [7] or even cessation of diuresis are not contraindications for kdn retrieval from NON-HBD. It might be argued, that we could shorten warm ischmia time by the installation of peritoneal cooling or immediate insertion of an aortic catheter for kidney flush as proposed by others [8]; however, these manipulations outside the operating room don't seem to be essential and would not be ethically accepted by our hospital personnel.

The striking finding of this analysis was the fact that most of the kdn's in the NON-HBD group were not lost for technical reasons (e.g. preservation failure) but due to acute vascular rejection, mostly associated with haemolytic uremic syndrome. It has to be emphasized that five of six such reactions developed in retransplants; three cases never showed function of the graft (PNF), one lost function after 12 days and two recovered permanently. This phenomenon remains unexplained, but we speculate that endothelial lesions in the graft, caused by prolonged warm ischemia, might intensify endothelial antigenic presentation giving rise to acute vascular rejection and thrombotic microangiopathy. As long as this finding of acute vascular rejection associated with haemolytic uremic syndrome in retransplanted kdn's from NON-HBD is not clarified, we propose to use kdn's from this source for first transplants only. Furthermore, we see here another good reason to avoid cyclosporine in the early postoperative period because it is known that cyclosporine can aggravate thrombotic microangiopathy. It is worth noting that four of six cases with this kind of rejection still had initial cyclosporine immunosuppression according to our former protocol. Within the last 2 years the number of kdn's from NON-HBD increased significantly and actually constitutes about 25% of all kdn grafts in our program. The results in this study showed that good short- and long-term results can be achieved with kdn's from this source.

We concluded that organ procurement from NON-HBD is an adequate approach to an important cadaver donor source that in general is not efficiently used, but could significantly increase the number of kdn grafts in most transplant programs. Successful patient and graft survival rates can be achieved if limited cold ischemia time is guaranteed, and initial immunosuppression with cyclosporine avoided. Results might improve with routine use of advanced preservation solutions and if kdn's of this origin are used for primary transplants only. There seems to be an increased risk of vascular rejection associated with hemolytic uremic syndrome in retransplanted kidneys from NON-HBD and this phenomeon needs to be investigated.

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