

Preliminary Results of Heart-beating and Non-heart-beating Donor Kidney Transplants-The Singapore Experience

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Abstract

Renal transplantation is the ideal renal replacement therapy for treatment of end stage kidney failure but its limitation is the constant shortage of cadaveric donors. While the traditional source of cadaveric kidneys is procurement from heart-beating donors, organ procurement from non-heart-beating donors (NHBD) would help in coping with the rising demand for organs. However various important legal, logistic and technical constraints have limited the implementation of such a procurement programme. Nevertheless, prolonged warm ischaemic times in procuring kidneys from NHB donors may affect the viability of these organs and adversely affect overall outcome after transplant.

Fifty-three consecutive patients who underwent renal allotransplantation (Tx) between January and December 1994 at the Singapore General Hospital were retrospectively reviewed. Outcomes after renal transplantation among 25 heart-beating donor (HBD) and 28 NHBD were compared. Despite significant differences in donor age (23.7 ± 11.0 and 34.1 ± 7.9 , $P = 0.001$), first warm (0 and 22.2 $\pm$ 9.0 minutes) and cold ischaemic times (12.8 ± 6.7 and 5.2 ± 5.0 hours, $P = 0.001$) between the HBD and NHBD groups, the two-year patient and graft survivals were very similar in both groups (100% versus 98% and 98% versus 96%). The incidence of delayed graft function (DF) was also comparable between the HBD (41%) and the NHBD (50%) Tx. These results suggest that NHBD is a viable source for kidney transplants and comparable patient and graft survivals can be achieved if the first warm and cold ischaemic times are kept to the minimum.

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Introduction

End stage renal failure (ESRF) is the most common end stage organ disease treated with transplantation in Singapore.¹ Though renal transplantation is the preferred treatment for ESRF, organ shortage is a major obstacle. At the end of 1997, 553 patients undergoing dialysis in Singapore were on the national waiting list for kidney transplants (Tx) but only about 25 cadaveric kidneys were transplanted in that year. While transplantation of kidney from heart-beating (HB) cadaveric donors is preferable, the problem of organ shortage has increased the need for expansion of the cadaveric donor pool. One possible source of kidneys for transplantation is the use of non-heart-beating (NHB) donors (NHBD) for cadaveric renal transplantation.

Cadaveric organs are subjected to multiple haemodynamic, metabolic and hormonal disturbances due to loss

of brainstem regulatory functions prior to organ harvest. Furthermore, ischaemic injury to organs may occur as a result of donor hypotension, donor cardiac arrest or even as a result of interruption of blood flow due to cross clamping of arterial supply at the time of organ harvest. This is termed as warm ischaemic injury as the organs are at higher risk for damage when subjected to ischaemia prior to cooling. A further source of injury is that which occurs due to prolonged cold storage and is termed cold ischaemic injury. While the severity and exact duration of ischaemic damage is often difficult to quantify precisely, it has been clearly established that both prolonged warm and cold ischaemia times are independent risk factors for worse cadaveric allograft function and survival.² Thus, in using NHB donors as organ donors, the duration of warm ischaemia is necessarily increased further as the duration of cardiac stand-

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still prior to organ harvest adds to the duration of warm ischaemia. This new pool of kidneys, therefore, does raise concerns regarding whether there is more delayed graft function and poor allograft survival. In this retrospective study, we analysed the early results of renal transplantation from HB and NHB donors, and the possible factors that might have affected their outcome.

Materials and Methods

Fifty-three kidney Tx were performed at the Singapore General Hospital between January and December 1994. Among these, 25 were harvested from HB cadaver donors, while 28 were from NHB cadaver donors.

All donor kidneys were harvested with the *in situ* preservation protocol as per the technique of Booster.³ After legal consent was granted, perfusion catheters were inserted in the operating theatre into the aorta proximal to the bifurcation. Selective perfusion of the part of the aorta at the origin of the renal arteries was obtained by ligating the upper end of the abdominal aorta just below the crus of the diaphragm. Another catheter was introduced into the vena cava to facilitate venous outflow.

In situ perfusion of the kidneys was performed with 8 to 10 litres cold Euro-Collins solution at 4°C, with the bag of solution being hung 1 m above the level of the donor, until the venous outflow was clear. The kidneys were palpated to ensure adequate cooling before simultaneous bilateral nephrectomy. Both kidneys were removed en bloc with the aorta and inferior vena cava. They were carefully inspected, reperfused with 1 to 2 litres of cold Euro-Collins and, if necessary, subjected to bench surgery. The kidneys were then preserved by the method of ice cold storage in Euro-Collins solution until they were transplanted at the earliest possible time to the selected recipient.

Cadaveric allograft recipients were selected from a national transplant register with allocation based on optimal histocompatibility and after taking into consideration other factors including waiting time, hepatitis status and level of pre-sensitisation.

Either dual (cyclosporin with prednisolone) or triple (cyclosporin, azathioprine and prednisolone) combination of immunosuppression were used initially. Rejection episodes were treated with methylprednisolone pulses as previously described.⁷

Donor and recipient demographics, patient and graft survival, the quality of graft function at discharge from hospital, 6, 12 and 24 months and surgical complications were respectively obtained by review of case notes. The post-transplant functions of each kidney were classified as immediate, delayed, or primary non function. Immediate function was defined as adequate allograft function obviating the need for post-transplant dialysis;

delayed function was defined by the need for dialysis post-transplant with eventual recovery in renal graft function; and primary non function was defined in an allograft that never had adequate function to be maintained off dialysis post-transplant. Warm ischaemic time was defined as the time interval from arterial clamping or cardiac standstill (whichever was earlier) to perfusion with cold Euro-Collins solution. Cold ischaemic time was defined as the interval from perfusion until release of clamps following anastomosis with recipient iliac vessels. Results were expressed as mean $\pm$ standard deviation. Statistical analysis of the donor and recipient data was conducted to compare baseline characteristics of NHB and HB groups. The independent sample t-test was used to compare differences between the groups for continuous variables and chi-square test with Yates correction or the Fisher exact test was used for comparison of differences between groups for discrete variables. Statistical significance was achieved with *P* values less than 0.05. All data were analysed by SPSS-PC Windows version 6.0 (1995).

Results

The study population comprised 31 males and 22 females with a mean age of 40.2 ± 8.8 years (range 17 to 56 years). The racial distribution was similar to that of the Singapore population; Chinese (47), followed by Malay (5) and Indian (1). In this series, 4 of the recipients had received a previous kidney transplant.

Table I summarises relevant donor data. Statistically significant differences between the two donor groups were found for the duration of mean first warm and cold ischaemic times. The first warm ischaemia time was zero minute in HBD as all of them received *in situ* perfusion with instantaneous cooling of kidneys, whereas for NHB the mean first warm ischaemic time was 22.2 minutes. However the mean cold ischaemic time was significantly different between the HBD and NHB groups at 12.8 h and 5.2 h, respectively (*P* = 0.01). Recipients of allograft from HB and NHB allograft donors were otherwise similar with respect to their demographic parameters as shown in Table II.

The outcome of renal transplantation in the two groups

TABLE I: DONOR DEMOGRAPHICS AND KIDNEY

	HBD	NHBD	<i>P</i> values
No. of donors	25	28	
Age (years)	23.7 ± 11.0	34.1 ± 7.9	0.01
Gender ratio (M/F)	23/2	25/3	0.74
Cold ischaemic time (h)	12.8 ± 6.7	5.2 ± 5.0	0.01
First warm ischaemic time (min)	NA	22.2 ± 9.0	0.01
Second warm ischaemic time (min)	24.9 ± 8.0	23.2 ± 10.2	0.79

HBD: heart-beating donors; NHBD: non-heart-beating donors

TABLE II: RECIPIENT DEMOGRAPHICS

	HBD (n = 25)	NHBD (n = 28)	P values
Age (years)	39.4 ± 9.7	41.1 ± 7.9	0.47
Sex (M/F)	15/10	16/12	0.21
Primary/retransplant	23/2	25/3	0.71
Dialysis type (HD/PD)	23/2	28/0	0.13
Duration of dialysis (months)	45.6 ± 27.9	54.9 ± 48.3	0.35
Mean creatinine at transplant (umol/L)	1193.6 ± 206.9	855.8 ± 294.4	0.40
Mean haemoglobin at transplant (g/dL)	8.4 ± 1.9	8.9 ± 2.1	0.38
HLA mismatches: A	0.76	1.1	0.17
B	1.28	1.2	0.72
DR	0.96	0.96	0.99

HBD: heart-beating donors; NHBD: non-heart-beating donors;
HD: haemodialysis; PD: peritoneal dialysis

TABLE III: RESULTS

	HBD	NHBD	P values
Immediate versus delayed graft function	14/10	13/14	0.47
Primary non-function	1	1	1.0
Creatinine (umol/L) at			
• discharge	120.2 ± 40.5	135.3 ± 50.6	0.34
• 6 months	122.0 ± 42.8	138.4 ± 51.8	0.23
• 1 year	130.9 ± 93.1	133.0 ± 39.5	0.92
• 2 years	139.4 ± 111.2	142.7 ± 42.8	0.89
2-year patient survival	100%	98%	0.34
2-year graft survival	98%	96%	0.93
Hospital stay (days)	17.9 ± 9.2	20 ± 9.6	0.43

HBD: heart-beating donors; NHBD: non-heart-beating donors

is shown in Table III. Overall actual two-year patient and graft survival rates were 98% and 96%, respectively. Two-year actual patient survival rate was 100% for the HBD group and 98% for the NHBD group because one patient died due to an unrelated cause ($P = 0.93$). The two-year actual graft survival was 98% for the HBD group and 96% in the NHBD group ($P = 0.47$). Delayed graft function was noted in 41% and 50% in the HB and NHB transplant groups, respectively. Primary non-function was found in one patient in each group. Mean creatinine at discharge, 6 months, 1 year and 2 years were similar in each group. No statistically significant difference was noted between the two groups in terms of patient and graft survival, delayed graft function, creatinine at follow up or the period of hospital stay.

Complications

One graft was lost in the HBD group due to acute rejection 2 weeks after transplant. It failed to respond to second line immunosuppressive therapy. Urinary tract

infection occurred in 2 patients which resolved with antibiotics.

One graft loss in the NHBD group was caused by venous thrombosis. Infectious complications developed in 4 patients (3 with urinary tract infection and 1 with wound infection). All infections responded to appropriate therapy. One patient suffered mild renal artery stenosis which was treated conservatively. Urinary calculi was found during follow up in one transplanted kidney and was treated by extracorporeal shock wave lithotripsy. Another recipient was later found to have stage 2 renal cell carcinoma in his native kidney after transplant and had radical nephrectomy performed shortly after diagnosis without sequelae.

Discussion

The major limitation of renal transplantation currently is the problem of shortage of cadaveric organ donors. As all organs harvested from cadaveric donors are susceptible to varying periods of ischaemia, one major strategy to optimising allograft function has been to minimise ischaemic injury. Thus, organs from non-heart-beating donors are not utilised in many centres because of concerns for the success rates of transplants from such sources as a result of the increased ischaemia sustained by such donor organs. However, to increase the donor supply, NHB donors were used as cadaveric renal donors initially in the United States, with increasing experience been gained in Europe^{4,11} and Southeast Asia^{1,12,13} recently.

In Singapore, kidneys from both the HBD and NHBD are used for renal transplantation. A more structured and positive legislation towards kidney transplantation in our society has helped to minimise any delay in obtaining consent and harvesting of organs. Rapid transfer of the donor to the operating theatre and *in situ* perfusion in the operating room followed by immediate perfusion of kidneys and bilateral nephrectomy is our method of choice in organ procurement. This has enabled us to achieve a relatively short first warm ischaemic time comparable to the double balloon triple lumen catheter method.³ Nevertheless, the quality of allograft function attained in kidneys from NHB donors is of concern.

The present study demonstrated that short-term graft and patient survivals of NHBD kidneys were comparable to that of HBD kidneys. These results were similar to those reported in other studies,^{9,10,13-18} but unlike the study by Wijnen et al¹⁶ which reported a significant higher percentage of delayed graft function in the NHBD group and therefore requiring longer hospital stay. Quality of graft function in terms of primary and delayed graft function, serum creatinine at two-year follow up and length of hospital stay were comparable in both groups. These important findings justify the use of kid-

neys from non-heart-beating donors. Furthermore Gonzalez et al¹⁹ have shown in their study, that kidneys obtained from NHBD can maintain and achieve long term function (up to 9 years follow-up) almost as well as kidneys from HBD.

One possible explanation for the comparable results between HBD and NHBD kidneys may have been the significantly shorter cold ischaemic times in the latter group. The NHBD kidneys from the present study had a minimal delay between diagnosis of death and organ procurement thus minimising warm ischaemia. Furthermore, special efforts had been made in transplanting NHBD kidneys at the earliest possible time as there had been concerns regarding the quality of kidney function from such kidneys. Thus, cold ischaemic times were significantly shorter in NHBD kidneys. Though the first warm ischaemic time was significantly longer in the NHBD group, this did not seem to have an adverse effect on the patient and graft survival as the cold ischaemia times were shorter in this group. As warm and cold ischaemic times are independent risk factors for adverse graft outcome, it is possible that the reduction in cold ischaemic injury ameliorated allograft injury and thus resulted in comparable graft and patient survivals in the two groups. Thus, while Cecka and Terasaki² have suggested from their analysis of multi-centre data that prolonged cold ischaemia beyond 36 hours had an adverse impact on long-term graft function, one may speculate that even small differences in cold ischaemic time may have an additive adverse impact on organs with prolonged warm ischaemia. Recent multivariate analyses have also shown that cold ischaemic time to be an independent risk factor causing delayed graft function and poorer graft survival.^{20,21} Likewise Schlumpf,¹⁵ Wijnen¹⁶ and Matsuno²² have suggested that cold ischaemic time should be kept to a minimum and ideally transplantation should be done within 12 to 24 hours for NHBD kidneys.

From the financial point of view, the set-up of NHB donor transplant programmes are also favourable. Not only is there a considerable saving on health costs when patients are free from long term dialysis, quality of life is generally better with more patients return to the work force.

Currently kidneys from NHBD represent about 32% of the renal transplant activity in our hospital. The results of outcome in kidneys from NHB donors are encouraging and suggest that NHBD is an important and viable alternative for kidney procurement. Good outcome after transplant for this group of recipients of NHBD kidneys can be achieved if measures are taken to shorten the warm and cold ischaemic times. Additional measures to further ameliorate ischaemic injury, for example, with calcium channel blockers, free oxygen radical scavengers and newer perfusion solutions may

further improve the outcome in such kidneys and need to be examined in a randomised controlled manner.

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