Early results of a controlled non-heart-beating kidney donor programme

Jacob A. Akoh1, Mark D. Denton1, Sharon B. Bradshaw1, Tahawar A. Rana1 and Martin B. Walker2

1South West Transplant Centre, Surgery & Renal Services Directorate and 2Intensive Care Unit, Critical Care Directorate, Plymouth Hospitals NHS Trust, Derriford Hospital, Plymouth PL6 8DH, UK

Correspondence and offprint requests to: Jacob A. Akoh; E-mail: jacob.akoh@phnt.swest.nhs.uk

Abstract

Background. We present our experience of a controlled non-heart-beating donation (CNHBD) programme in a University Hospital.

Methods. Data from all referrals for CNHBD between January 2005 and January 2008 were collected prospectively. Donor and recipient data were analysed and compared to other cadaveric and HBD transplants performed during the same period.

Results. During the period, 79 donors were referred resulting in 35 proceeding to retrieval and 61 kidneys being successfully transplanted. The median time from withdrawal of therapy to asystole was 15 min (IQR 10.0–23.0). The median primary warm ischaemic time was 20 min (IQR 16.0–27.0). The mean cold ischaemia time was 16.6 ± 4.21 h for CNHBD (16.6 ± 5.91 for HBD) kidneys. Compared to HBD kidneys, CNHBD kidneys had more HLA mismatches and significantly more delayed graft function (44% versus 14%), and the mean time to halving of serum creatinine was significantly greater (12.8 versus 5 days). However, 1-year patient and graft survival (88% and 93%) were excellent and mean creatinine at 12 months for CNHBD kidneys was not significantly different from HBD kidneys (12.8 versus 5 days).

Conclusions. Structured implementation resulted in a successful CNHBD programme providing 61 successful renal transplants from 35 donors in 3 years—contributing to ∼50% of the total number of cadaveric renal transplants during the period. At 12 months, CNHBD kidney graft function was equivalent to HBD organs.

Keywords: asystole; controlled non-heart beating donor; delayed graft function; discard rate; renal transplantation

Introduction

The number of patients waiting for renal transplantation has continued to rise over time. In the UK, the waiting list has increased by 51% over the last 10 years [1]. The continued mismatch between supply and demand for organs has led to the development of controlled non-heart beating donor or donation (CNHBD) programmes in the UK and other parts of the world. The proportion of total transplant activity in the UK due to non-heart-beating donors has increased steadily over the last decade [1]. Between April 2006 and March 2007, there were 159 CNHBDS yielding 307 kidneys for transplantation in the UK. Key considerations in establishing a CNHBD programme include the difficulty in predicting asystole, potential ethical and logistical difficulties relating to the process and the outcomes of CNHBD organs. Most UK non-heart-beating donor (NHBD) programmes are CNHBD where donation occurs after a planned withdrawal of organ support in a critical care environment rather than the uncontrolled retrieval following failed resuscitation. Previous reports of programmes obtaining NHBD organs for renal transplantation have shown that NHBD consistently increase the number of available kidneys [2–4]. Though long-term results are similar to kidneys from heart beating donors (HBD), the short-term outcomes are worse in terms of a higher rate of primary non-function (PNF) and delayed graft function (DGF) [3–7]. These reports do not clearly differentiate between controlled and uncontrolled NHBD.

The South West Transplant Centre (SWTC) serves a population of 2.2 million and is located within a large university teaching hospital of 860 beds with an Emergency Department treating ∼75 000 patients per annum. There are 19 general critical care beds, including four neurosurgical critical care beds plus 8 beds in a separate Cardiothoracic Intensive Care Unit. We present our experience implementing a CNHBD programme and the subsequent results after 3 years.

Subjects and methods

Prior to commencement of the CNHBD programme, a steering group comprising the main stakeholders studied the concept and associated processes and reported that it was feasible in terms of potential organ yield and availability of resources. Next, an implementation group identified the precise resources required for a successful programme and constructed a detailed protocol for the key processes involved in each donation from referral to retrieval and subsequent transplantation. The SWTC obtained funding from UK Transplant (now part of NHS Blood & Transplant) on an annual recurring basis for an initial 3-year period—now extended for another 3 years. The shortfall in funding was made up by the Local Specialist Commissioning Group. The CNHBD programme commenced in January 2005 and all referrals between January 2005 and January 2008 are included in this analysis. The initial absolute contraindications to the selection of potential donors are shown in Table 1. After the first year, age was considered as a relative contraindication.
All patients received comfort therapy following the decision to withdraw multi-organ support. Following asystole, a stand off time of 10 min was observed. During the first 5 min, the nursing staff would explain to the family that the patient has died and remind them of the time of transfer to the operating theatre. During the second 5 min, the patient would be transferred to theatre while the staff prepared for intervention. The “super rapid” laparotomy technique and insertion of a double balloon catheter via the iliac artery was the surgical technique used in this series. Double balloon catheters were not used for multi-organ retrieval (liver, pancreas and lungs)—performed during the later stages of the study period. Thirty-nine of the retrieved kidneys were stored in a LifePort™ perfusion machine and 22 in cold storage. Only kidneys randomized to cold storage as part of the Pulsatile Perfusion in Asystolic donor Renal Transplantation (PPP ART) trial [8] or where the artery had no Carrel’s patch were preserved by cold storage in this series.

Retrieved kidneys were discarded on clinical grounds only. Machine parameters were not used to select or discard kidneys. CNHBD kidneys were offered to patients who had previously indicated their willingness to accept such kidneys (consents obtained either from patient surveys or at entry on transplant waiting list). Patient selection was based on the agreed local allocation policy (best HLA match, age, low matchability scores, etc. ethnic minorities, long waiting times and health status) effected by UK Transplant (now part of NHS Blood and Transplant).

Immunosuppression comprised basiliximab (induction), tacrolimus (0.1 mg/kg/day), mycophenolate acid (2 g/day) and prednisolone. The follow-up after recipient discharge was according to the routine practice in the unit.

For each donor referral, the cause of death, timing of withdrawal of treatment, parameters relating to levels of organ support, the withdrawal–asystole interval and any reason for not proceeding to donation were recorded. The interval from asystole to cold perfusion (primary warm ischaemic time [WIT]), the total WIT (defined as time from systolic blood pressure of <50 mmHg to perfusion) machine perfusion, organ usage or discard, cold ischaemia time (CIT), incidence of delayed graft function (defined as requirement for dialysis within the first 2 weeks post-transplant) and acute rejection were analysed. The transplants performed between January 2005 and December 2007 (57 CNHBDs and 58 cadaveric HBDBs—excluding 44 living donor transplants) were analysed for comparison. Human leukocyte antigen (HLA) mismatches, cold ischaemia time, early and late graft function, time to halving of serum creatinine (Cr) level, Cr at 3, 6 and 12 months, 1-year patient and graft survival were compared for transplants during the period of the study.

The difference in the incidence of DGF between kidneys preserved by machine perfusion or cold storage was tested by the \( \chi^2 \) statistic with a \( P \)-value of <0.05 taken as significant. Also the differences in rates of DGF and biopsy-proven acute rejection between types of donor were tested by the \( \chi^2 \) statistic. The differences between the mean CIT, HLA mismatches and time to halving serum Cr were analysed by the one-sample \( t \)-test with the two-tailed \( P \)-value of <0.05 being taken as significant.

**Results**

Seventy-nine potential donors were referred for CNHBD (Maastricht type III) resulting in 35 (18 females, 17 males) proceeding to retrieval and 61 kidneys being successfully transplanted. The reasons why 44 patients did not proceed to organ donation are shown in Table 2. Among the 35 proceeding to organ donation, the cause of death was intracranial haemorrhage [18], hypoxic encephalopathy [9], traumatic brain injury [5], myocardial infarction [1], suicide [1] and multiple trauma [1].

The median age of the donors was 54 years (range 11–71) with four over 65 years. When critical care organ support was withdrawn, 77% (27/35) were maintained on inspired fraction of oxygen <50%, and 89% (31/35) required positive end-expiratory pressure of only 5 cm H2O. Forty-nine percent of donors (17/35) required little or no vasopressor support, and 83% (29/35) were extubated as part of the withdrawal of treatment process. These parameters were similar to the group not proceeding to donation.

A standoff time of 10 min was observed in all cases. The median time from withdrawal of life sustaining therapy to asystole was 15 min (IQR 10.0–23.0). Other donor parameters are shown in Table 3.

Nine kidneys were discarded after retrieval. Two kidneys from a 71 year old were rejected because they were small and scarred—these kidneys were neither biopsied nor considered suitable for en bloc transplantation. Two other kidneys from a 70 year old were not used as the post-retrieval biopsy unexpectedly made the diagnosis of metastatic small cell carcinoma of the lung. Two kidneys (donors aged 63 and 67 years) were rejected due to 80% stenosis in the renal arteries, and one kidney from a 58-year-old donor was discarded due to a venous anomaly, which was not considered reconstructable. The remaining two kidneys from an AB blood group donor (aged 56 years) could not be used as there were no suitable local or national recipients.

**Table 1.** Initial absolute contraindications to CNHBD

<table>
<thead>
<tr>
<th>Classification</th>
<th>Number of patients</th>
<th>Description of contraindications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age &lt; 16 or &gt; 65 years</td>
<td></td>
<td></td>
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<tr>
<td>HIV infection</td>
<td></td>
<td></td>
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<tr>
<td>CJD</td>
<td></td>
<td></td>
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<tr>
<td>Malignancy except primary CNS tumour</td>
<td></td>
<td></td>
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<tr>
<td>Untreated septicemia</td>
<td></td>
<td></td>
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<tr>
<td>Recipient of human tissue/organ transplant</td>
<td></td>
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</tr>
<tr>
<td>Untreated or uncontrolled hypertension or organ damage from hypertension</td>
<td></td>
<td></td>
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<tr>
<td>Diabetes mellitus with end organ damage</td>
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<td></td>
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<tr>
<td>Recipient of human growth hormone or fertility treatment prior to 1985</td>
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</tbody>
</table>

**Table 2.** Reasons for patients not proceeding to CNHBD following referral

<table>
<thead>
<tr>
<th>Classification</th>
<th>Number of patients</th>
<th>Description of contraindications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Delayed asystole</td>
<td>15</td>
<td>Patient reviewed and procedure normally abandoned after 2 h if asystole has not occurred</td>
</tr>
<tr>
<td>Early asystole</td>
<td>4</td>
<td>Asystole prior to consent (3) Asystole prior to retrieval team arrival (1)</td>
</tr>
<tr>
<td>Family declined consent or absence of nominated representative or person in qualifying relationship</td>
<td>10</td>
<td>Family changed mind (2) Family knew patients wishes (3) Internal family conflict over donation (4) Absence of qualifying individual (1)</td>
</tr>
<tr>
<td>Medical unsuitability</td>
<td>14</td>
<td>Malignancy (5) Significant vascular disease (4) Acute pancreatitis (1) Neurological condition of unidentified aetiology (1) Untreated sepsis (1) Chronic renal impairment (1)</td>
</tr>
<tr>
<td>Brain stem death intervened</td>
<td>1</td>
<td>Multiple co-morbidities (1) Proceeded to multi-organ donation</td>
</tr>
<tr>
<td>Total</td>
<td>44</td>
<td></td>
</tr>
</tbody>
</table>

1993
Table 3. CNHBD Graft parameters

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Plymouth data</th>
<th>UKT summary data (where available)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time from withdrawal to asystole (minutes)</td>
<td>Median (IQR) [61 renal grafts]</td>
<td>Median (IQR) [No. of renal grafts]</td>
</tr>
<tr>
<td>Primary warm ischaemic time (minutes)</td>
<td>15.0 (10.0–23.0)</td>
<td>15.0 (12.0–18.0) [774 grafts]</td>
</tr>
<tr>
<td>Total primary warm ischaemic time (minutes)</td>
<td>20 (16.0–27.0)</td>
<td></td>
</tr>
<tr>
<td>Asystole to perfusion</td>
<td>16.05 (13.8–20.4)</td>
<td>17.9 (14.5–21.5) [804 grafts]</td>
</tr>
<tr>
<td>Mean 12-month creatinine (µmol/l)</td>
<td>141</td>
<td></td>
</tr>
</tbody>
</table>

Forty-one percent (16/39) of the kidneys preserved by machine perfusion showed delayed graft function compared to 45% (10/22) of kidneys preserved in cold storage. This difference was not statistically significant ($\chi^2 = 0.004$; 1 DF; $P = 0.9471$).

Table 4 shows a comparison of various factors according to the type of allograft. Primary non-function was not observed in the CNHBD group. There was a significantly greater incidence of DGF in the CNHBD group compared to the HB group (44% versus 14%). There were five deaths in the CNHBD group over a mean 20-month follow-up period (two from myocardial infarction, one from sepsis, one from post-transplant lymphoproliferative disease and one from undetermined cause) compared to four deaths in the HBD group. Two recipients of CNHBD kidneys lost their grafts over a mean 20-month follow-up period (one from chronic humoral rejection and one from recurrent focal segmental glomerulosclerosis). The mean serum Cr at 1 year post-transplantation was 141 µmol/l. Figure 1 illustrates the serum creatinine level at 3, 6 and 12 months post-transplantation.

**Discussion**

The continuing discrepancy between supply and demand for organs has led to re-examination of the case for organs from non-heart beating donors. Improvements in the techniques of organ retrieval, perfusion and recipient management across the board have made the use of organs from such donors feasible. However, in a recent review of the medical and ethical issues relating to retrieval of NHBD in Canada, Doig et al. [9] concluded that the call for a moratorium on local NHBD protocols should continue until a Canadian national consensus emerged. They recognized the potential for increasing organ and tissue donation but felt that progress should be based on sound ethical and legal principles and not just on the need to match ‘supply’ with ‘demand’. In the UK, the situation is different, with UK Transplant actively supporting transplant units to develop a CNHBD programme. The British Transplantation Society (BTS) has also produced a consensus statement supporting CNHBD and summarizing the ethical considerations [10]. The Intensive Care Society has also published guidelines...
for CNHBD and supports it as a means of increasing donor numbers. In view of the logistical and ethical considerations of CNHBD, it is important prior to establishing such a scheme to make adequate preparations. Our experience shows that a well-designed service delivery process can result in a successful programme. During the period under review kidneys from non-heart beating donors contributed 36% (57/159) of the overall transplant activity and resulted in a steady rise in transplant activity over 4 consecutive years. Early identification and involvement of stakeholders, especially including the Coroner (an official responsible for investigating and determining the cause of deaths), contributed to successful implementation and a boost to transplantation activity. Furthermore, the local potential donor audit raised the probability that half of the donor activity would take place during normal working hours thereby disrupting elective or emergency theatre activity. Probably because of the extensive consultations prior to launching the programme, there were no major problems in getting the support of the hospital staff. Surgeons were willing to allow scheduled operating lists to be cancelled in order to make CNHBD and hospital management was also willing to accept the loss of this other theatre activity.

Even with a successful CNHBD programme, it may be possible to improve the numbers of successful transplants. Eighty-seven percent of kidneys retrieved from 35 donors were successfully transplanted. This discard rate of 13% is comparable to the 15% reported by Casavilla et al. [11] in their subgroup of CNHBDs and the 15.6% by Reiner [12]. It is interesting that six of the nine kidneys discarded (67%) were from donors aged over 63 years. Excluding kidneys from the 56-year-old AB donor and the 58-year-old donor with a deficient vein, five of six kidneys discarded were from donors aged over 65 years. It would appear that limiting the cut-off donor age to 65 might improve the discard rate.

There are other advantages of using younger donors. Snoeijs et al. [13] reported that grafts from older donors (over 65) were associated with inferior glomerular filtration rates and graft survival and recommended that use of such kidneys should only follow histological assessment of pre-transplant biopsies.

It might be possible to improve the donation rate by reducing factors that prevent donation (Table 2); however, despite the best efforts of intensive care clinicians and transplant co-ordinators, it is proving difficult to influence the family refusal rates and it is too early yet to know if changes in legislation (Human Tissue Act, 2004 and Mental Capacity Act, 2005) may influence this. In a study to explore why family members decline organ donation from a deceased relative, protecting the body (keeping the body whole and intact) was the most frequently recurring theme [14]. More concerted efforts at supporting bereaved families in understanding the donation process and in balancing the emotions of giving the ‘gift of life’ with the perceived ‘sacrifice’ of organ donation may increase the number of families assenting to donation.

A stand-by time (agonal period) of 2 h was decided upon after considerable discussion during the planning phase. Less than half of the potential donors referred proceeded to asystole within 2 h. Our general experience is that potential CNHBDs who are not asystolic within the 2-h period frequently continue to have a cardiac output for a considerable amount of time. However, Sohrabi et al. [15] have shown that it is possible to extend the stand-by time beyond 2 h provided the kidneys retrieved pass viability assessment using machine perfusion. Such kidneys must demonstrate appropriate pressure-flow characteristics and perfuse enzyme levels. With this technique, they have successfully transplanted 16 kidneys retrieved from donors with an agonal period in excess of 2 h, but the discard rate was high—13% if <2 h; 33% if >2 h and 45% if >5 h.

Despite the fact that both kidneys were retained within the centre, the mean cold ischaemia times for CNHBD and HBD kidneys were similar (Table 4). Sanni et al. [6] also reported similar (but higher) cold ischaemia times for their NHBD and HBD kidneys. Our local protocol requires the kidneys to be removed from the donor before they can be allocated. As was the case in our centre, the two kidneys from any given donor were implanted sequentially. The shorter cold ischaemia time of the first transplant may be counter-balanced by the longer time for the sister kidney.

The incidence of DGF (44%) in this series is similar to the report of some authors [6,16] and compares to the UK average (Table 3), but superior to other reports [2,5]. This is possibly because the UK summary data and indeed many authors include uncontrolled and controlled non-heart beating kidney transplants in their results. This study deals exclusively with CNHBD and this in addition to other strict criteria employed may account for the low DGF rate. Analysis of the incidence of DGF with respect to the kidney storage method did not reveal any significant differences. This is in agreement with the PPART trial interim report [17] and raises the question whether machine perfusion is necessary. However, the European trial results suggest that machine perfusion confers benefit on kidney function with reduced DGF and better 1-year survival [18]. Registry data from North America show that discard rates and DGF were lower in machine perfused kidneys [19,20]. Further studies are required to resolve the role of machine perfusion in NHBD kidneys.

The poor HLA matching of non-heart beating kidneys in this centre is a direct result of the allocation policy of retaining both kidneys in the centre. Despite worse HLA matching, acute rejection rates were equivalent perhaps due to the use of potent maintenance immunosuppressive therapy. An alternative explanation is that in the absence of brain stem death and the resultant cytokine storm these kidneys were less immunogenic.

Figure 1 and Table 4 show that the immediate to medium term function of these kidneys is satisfactory and in fact comparable to kidneys retrieved from heart-beating donors. Transplant function is equivalent irrespective of the donor source. Due to the successes of the CNHBD programme, the programme has been extended to include liver and pancreas retrieval (performed by a Regional Liver Unit) and retrieval from five other intensive care units in the South West of England.

The successful implementation of a CNHBD programme at the SWTC has its roots in the meticulous planning including a feasibility study, identification of resources required,
development of protocols and careful consideration of the legal and ethical implications. CHNBD has boosted the transplant activity of the centre by 30%. The early results from this programme are excellent but caution in extending the barriers to include donors over 65 years should be exercised. This study shows that CNHBD kidneys from donors aged <65 years perform as well as HBD kidneys.

Acknowledgements. We thank UK Transplant for providing data on CNHBD kidney graft outcomes and for granting SWTC financial support to start the programme. We acknowledge the contributions of the Steering Group (J. A. Akoh, R. Stoddard-Murden, P. A. Rowe, M. Roy, M. B. Walker, N. Meadows, C. Andrews, T. Kyriakides-Yeldham, I. Wren, J. Leary and R. Gair) and the Implementation Committee (J. A. Akoh, P. Rowe, R. Stoddard-Murden, R. Gair, M. B. Walker and E. Richardson) towards the establishment of CNHBD in Plymouth, UK.

Conflict of interest statement. None declared.

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Received for publication: 3.10.08; Accepted in revised form: 3.2.09