Protocol

Quality assessment of Human Kidneys by *Ex-vivo* Normothermic Perfusion prior to Transplantation

Professor Michael L Nicholson

Department of Surgery, University of Cambridge

Summary

Approximately 10 to 15% of kidneys are donated and surgically retrieved for transplantation but then deemed unsuitable and therefore discarded. The decision not to transplant an organ is made by an experienced Transplant Consultant based on factors such as the history of the donor, the ischaemic interval and quality of the *in-situ* perfusion. However, many of these kidneys may actually be suitable for transplantation. *Ex-vivo* normothermic perfusion (EVNP) is a technique of preservation that involves warming the kidney to normal body temperature with an oxygenated red blood cell based solution. It has been shown to improve the outcome of kidneys from older and marginal donors. It is also a valuable device on which to assess the quality of a kidney before transplantation. Adopting this system to assess the quality of a kidney could potentially allow more kidneys to be transplanted. We aim to assess the quality of kidneys that have been declined for transplantation by other transplant centres through the national allocation system and through the fast-tracking system. If they are deemed suitable they will transplanted into an appropriately matched recipient.

Background

Approximately 10 - 15% of kidneys are donated but then declined for transplantation by transplant centres [1]. The reasons for declining a kidney are multifactorial but include donor history, duration of cardiac arrest, quality of *in-situ* perfusion, the duration of hypothermic preservation, sub-optimal perfusion characteristics during hypothermic machine perfusion, chronic changes on histological analysis, and a visual inspection of the kidney. Ultimately, the decision relies on the judgement of experienced Transplant

Consultants but is subject to varying opinion. A more robust assessment of kidney function prior to transplantation would be a more precise way of determining the suitability of a kidney for transplantation.

The preservation period offers the ideal situation in which to assess the organ and determine its quality. This has several advantages; it may allow us to predict post-transplant function, prevent the use of non-viable kidneys and make more kidneys available for transplantation.

Assessment of viability under hypothermic techniques is limited. However, *ex-vivo* normothermic perfusion (EVNP), a technique of preservation that involves warming the kidney to near-normal body temperature with an oxygenated red blood cell based solution, may offer that opportunity. EVNP was introduced into clinical practice in Leicester in December 2010 [2]. We have now successfully transplanted 36 kidneys after EVNP [3]. The concept is to restore renal metabolism under ideal conditions and regain function for a short period before transplantation to reduce ischaemic injury and improve early graft function. Preliminary results have demonstrated its safety and feasibility with no technical difficulties or adverse events after transplantation [2, 3]. Similar techniques have been used to assess and transplant previously rejected lungs [4] and more recently to assess discarded human livers [5].

In a laboratory based study we have assessed the viability of 92 discarded human kidneys during 60 minutes of EVNP. This has provided valuable information about the efficacy of EVNP in predicting viability. We have developed an assessment system whereby kidneys can be graded on the basis of their macroscopic appearance and perfusion parameters (Appendix 1). Kidneys are graded from 1 (indicating the best quality) to 5 (the worst quality). In the financial year 2013-2014 a total of 262 human

kidneys retrieved in the UK were not transplanted due to concerns about quality or viability. A crude estimate of the influence of EVNP on discard rates can be made on the assumption that kidneys scoring 1-4 can be successfully transplanted. These comprised 81% of our series and if this scaled up to a national level at total of 212 additional kidneys transplants could have been performed. This would represent an annual increase in the transplant rate of 10%.

Aim

The aim of this study is to increase the number of kidneys for transplantation by using EVNP to assess the quality of kidneys that have been declined by other centres and would otherwise be discarded. If deemed suitable they will be transplanted into an appropriately matched recipient.

Principal Inclusion Criteria

1: Kidneys declined for transplantation by several transplant centres and by all the fast-track transplant centres due to adverse donor characteristics, prolonged ischaemia, gross appearance, histological changes (excluding cancer), and cold perfusion parameters.

2: Donor and recipient age ≥ 18 years

3: Patient undergoing a 1st or 2nd renal transplant from a deceased donor.

4: Written, signed informed consent to the procedure.

Exclusion Criteria

1: Kidneys that are deemed unsuitable for transplantation due to contraindications defined by current NHSBT criteria [6].

2: Kidneys with irreparable vascular damage.

3: Recipients of a 3rd or subsequent transplant.

Study Monitoring

The results will be prospectively reviewed after every procedure. Any adverse events will be recorded. Patients will remain in the study until they are discharged after the transplant procedure. They will continue to be followed up closely throughout the lifespan of their kidney.

Methods

In agreement with NHSBT, the kidneys utilised in this study will have been allocated by the National Kidney Allocation Scheme and through the fast-tracking system but subsequently declined for transplantation by several transplant centres. Consent from the donor family for the use of the organs for transplant will have been obtained by the specialist nurses in organ donation (SN-OD) before organ retrieval. Consent will also be taken from the transplant recipient.

Allocation of kidneys

Kidneys will be offered through the NKAS by NHSBT and the fast-tracking system. Once NHSBT has deemed a kidney to be unplaceable it will be offered to a suitable recipient

on the Cambridge, Newcastle, or Guy's transplant waiting list (depending on which centre has the patient with the highest points score using the NKAS). The centre will have the freedom to implant the kidney into whichever patient they wish, not necessarily the highest scoring patient. This ensures use of these highly marginal kidneys in an appropriate recipient based on clinician judgement, rather than the computer-based allocation algorithm.

All patients meeting the inclusion criteria will be given a patient information sheet and will have the technique explained to them before surgery. Written informed consent will be obtained.

On arrival at the transplant centre, kidneys will undergo a period of EVNP under aseptic conditions in the operating theatre to assess perfusion parameters.

The recipient will be prepared for the transplant procedure in the usual way. If the kidney is deemed suitable for transplantation (using the scoring system described below, and after careful assessment by the transplant team) the patient will be anaesthetised and then undergo the transplant procedure.

Ex-vivo Normothermic Kidney Perfusion (EVNP)

The kidney perfusion system has been designed using paediatric cardiopulmonary bypass technology. Kidneys will be prepared and the renal artery, vein and ureter cannulated.

The circuit will be primed with a perfusate solution (Ringer's solution, Baxter Healthcare) and supplements added to provide a physiological environment. One unit of

blood group compatible and cross-matched packed red blood cells from the local blood bank will be added to the priming solution.

The kidneys will be perfused with red cell based solution at a set mean arterial pressure and near-normal body temperature. Supplements will be infused into the venous reservoir and arterial arm of the circuit to maintain normal homeostatic conditions.

The renal blood flow (RBF) and mean arterial pressure (MAP) will be recorded continuously and intra-renal resistance (IRR) calculated (MAP/RBF). Urine will be collected and output measured throughout perfusion. Blood gas analysis of arterial and venous blood will be used to record acid-base homeostasis and measure oxygen consumption.

Routine biochemistry and haematology will be used to assess renal function. A sample of plasma and urine will be frozen and kept for the analysis of biomarkers. A protocol transplant biopsy will be taken as normal practice before EVNP and after 30 minutes of reperfusion for routine histological assessment and molecular analysis.

Patient Assessment & Outcomes

Early and intermediate graft function

- Daily serum creatinine levels to measure creatinine fall over the first 7 days then at 1 and 3 months after transplantation
- eGFR; day 7 and 14, 1 and 3 months
- Rates of delayed graft function (DGF); Defined as the need for dialysis within the first 7 days after transplant

- Slow graft function rate (SGF); Defined as a less than 10% reduction in serum creatinine levels within for 3 consecutive days after transplantation.
- Rates of primary non function (PNF); Defined as the graft never functioning.
- Episodes of acute rejection within the first 3 months. Categorised into cell mediated and antibody mediated rejection.
- Adverse reactions eg infection, thrombosis of the graft
- Length of hospital stay
- Perfusion parameters during EVNP (renal blood flow, urine output)
- Histopathology, molecular markers
- Quality of life assessment (Kidney disease Quality of Life – short form)

Longer term outcome

- Serum creatinine levels at 6 and 12 months
- eGFR levels at 6 and 12 months
- Number of rejection episodes
- Incidences of graft loss

Quality of Life

Quality of life shall be measured using the kidney disease quality of life short form (KDQoL-SF) [7]. The questionnaire will be given before transplantation and at 3 months post-transplant.

Renal transplant biopsy

A biopsy will be taken from the kidney pre-implantation, after reperfusion and, where possible, at 3 months post transplant. The 3 month biopsy will be performed under local anaesthetic on the day case ward.

References

1: Callaghan CJ, Harper SJ, Saeb-Parsy K, Hudson A, Gibbs P, Watson CJ, Praseedom RK, Butler AJ, Pettigrew GJ, Bradley JA. The discard of deceased donor kidneys in the UK. Clin Transplant. 2014 Mar;28(3):345-53.

2: Hosgood SA, Nicholson ML. First in man renal transplantation after *ex vivo* normothermic perfusion. Transplantation. 2011 Oct 15;92(7):735-8.

3: Hosgood SA. Renal Transplantation After Ex Vivo Normothermic Perfusion: The First Clinical Study. Am J Transplant. 2013 Feb 22.

4: Wallinder A, Ricksten SE, Hansson C, Riise GC, Silverborn M, Liden H, Olausson M, Dellgren G. Transplantation of initially rejected donor lungs after ex vivo lung perfusion. J Thorac Cardiovasc Surg. 2012 Nov;144(5):1222-8.

5: Op den Dries S, Karimian N, Sutton ME, Westerkamp AC, Nijsten MW, Gouw AS, Wiersema-Buist J, Lisman T, Leuvenink HG, Porte RJ. Ex vivo Normothermic Machine Perfusion and Viability Testing of Discarded Human Donor Livers. Am J Transplant. 2013 May;13(5):1327-35.

6: http://odt.nhs.uk/pdf/contraindications_to_organ_donation.pdf

7: Barotfi S, Molnar MZ, Almasi C, Kovacs AZ, Remport A, Szeifert L, Szentkiralyi A, Vamos E, Zoller R, Eremenco S, Novak M, Mucsi I. Validation of the Kidney Disease Quality of Life-Short Form questionnaire in kidney transplant patients. J Psychosom Res. 2006 May;60(5):495-504.