Summary Protocol

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Background

Introduction

Chronic kidney disease requiring renal replacement therapy affects 44,000 adult patients in the UK, a population that is growing at 6% per annum. Kidney transplantation remains the best form of renal replacement therapy for many of these patients. In the UK the prevalent kidney transplant population is approximately 20,000; the remainder of those needing renal replacement therapy are treated by dialysis. There is an increasing demand of recipients for kidney transplants, due not only to the increase in incident cases, but also from those patients whose transplanted kidney has failed; this occurs in 3% of the prevalent transplant population, resulting in approximately 600 patients per year returning to the transplant list. However, the supply of kidneys for transplantation is more or less static, so that between 1997 and 2007, the number of patients in the UK waiting for a transplant increased by 43%. By 2007, this amounted to 6,480 patients, of which only 17% (1,440) received a kidney in 2007. The picture is similar in other European countries. The consequences for a patient deemed best treated by transplantation of remaining on or returning to the transplant list are substantial; not only is there significant morbidity of dialysis but appreciable annual mortality (approximately 3%) among these patients. This is in addition to the cost of dialysis (£31,000 per patient per year in 2007), consuming approximately 1% of the NHS budget. Therefore, approaches that maximise the lifespan of each transplanted kidney will benefit patients directly, contribute to a reduction in the transplant list and moderate the costs of renal replacement therapy. This research protocol will evaluate the efficacy of an intervention that we hypothesise will improve the chances of early and late success of renal transplantation.

Renal injury is caused by ischaemia and reperfusion during transplantation

In many renal transplants, the kidney is exposed to warm ischaemia prior to harvest, cold ischaemia caused by the delay in transplanting the harvested organ, and a further period of warm ischaemia during the transplantation procedure. Cell death follows interruption of the blood supply to the kidney and successful reperfusion is mandatory for tissue salvage. Whilst this may be an integral part of the healing process, it may also contribute to tissue injury. Therefore tissue damage is a composite of injury that occurs during ischaemia and reperfusion; so-called ischaemia-reperfusion (IR) injury. The degree of IR injury determines the speed of recovery of organ function in the short term, and is most significant following non-beating-heart transplantation. In addition, it may modulate organ rejection in the longer term by priming the immune response early after transplantation. Reduction in IR injury has potential to improve the outcome of kidney (and other organ) transplantation, in the short and long-term.

Ischaemic preconditioning reduces IR injury

Ischaemic preconditioning (IPC) utilises sub-lethal ischaemia (preconditioning stimulus) to induce a state of protection against subsequent prolonged ischaemia. There are 2 phases of protection. There is a phase of IPC occurring within minutes of the preconditioning stimulus and lasts for up to 4 hours. The mechanism of early IPC has been extensively studied in animals and involves mediators that are generated during hypoxia (e.g. adenosine), a cascade of second messengers (e.g. phospholipases and kinases), and end effectors, including ATP-sensitive potassium channels and the mitochondrial permeability transition pore. A late phase of IPC occurs 24 hours after the preconditioning stimulus, which lasts for up to 72 hours and is termed the “second window of protection”, distinguishing it from early IPC. The prolonged (24-hour) interval between the preconditioning event and its renewed protection one day later is consistent with new protein synthesis (including heat shock and other cytoprotective proteins). Although the majority of studies to date have demonstrated protection by

IPC against IR injury to the myocardium of animals and humans, a smaller number of studies have investigated the potential of IPC to protect other organs, including the kidney. In animal models IPC attenuates injury and preserves function following renal IR and after renal transplantation.

Remote ischaemic preconditioning

Despite the 20 years that have elapsed since the first description of IPC, its therapeutic value in the clinical setting remains untested. This is largely due to the logistical difficulties of applying ischaemic stimuli to induce preconditioning in vital organs in humans. Nor has it yet been possible to induce IPC pharmacologically, a reflection of the incomplete understanding of the mechanisms and the likelihood that multiple biological targets need to be activated. Demonstrating that there is clinically relevant tissue protection would stimulate renewed interest in pharmacological approaches to modulate ischaemic preconditioning.

However, the realisation that IPC protects tissues that are distant from those undergoing preconditioning has led to recent interest in direct clinical application of IPC. This facet of preconditioning (termed remote ischaemic preconditioning; RIPC) has been shown to be protective against IR injury of the myocardium, skeletal muscle, small intestine and kidney. RIPC is mechanistically similar to IPC and causes a similar degree of tissue protection, as does IPC. The preconditioning signal is spread systemically by a mechanism that includes activation of the autonomic nervous system, and as yet unidentified humoral mediators.

We were the first group to show that RIPC could be triggered by limb ischaemia, and reduce experimental myocardial infarct size in pigs. Subsequent studies by our group and by others have determined that short periods of limb ischaemia also induce RIPC in humans. Therefore it may be possible to induce ischaemic preconditioning in the kidney using a remote stimulus such as limb ischaemia. This clinical study will test this possibility, and determine whether transient periods of limb ischaemia can induce a protective state to reduce renal IR injury that occurs following living-donor renal transplantation.

Primary objective

To determine whether RIPC improves glomerular filtration rate of the transplanted kidney in adults 12 months after undergoing living-donor transplantation.

Secondary objectives

To determine the effects of RIPC on:

1. Rate of fall in creatinine in the first 72 hours after transplantation
2. Inflammatory response to surgery in the first 5 days after transplantation
3. Protein expression in kidney parenchyma samples using histochemistry
4. Protein activation and expression in renal vasculature using immunoblotting
5. Kidney fibrosis 6 months after transplantation
6. Alloreactivity of T cells in the first 18 months after transplantation
7. Patient outcomes 2-5 years after transplantation using renal registry data

Sample size

400 living-donor renal transplant patients.

Inclusion criteria

1. Patients undergoing living donor-transplantation

2. Patients aged 18 years and above.

Exclusion criteria

1. Patients on ATP-sensitive potassium channel opening or blocking drugs
2. Patients on ciclosporin
3. Patients with a known iodine sensitivity (who cannot undergo iohexol clearance studies)
4. Patients with ABO incompatibility
5. Any patient requiring HLA antibody removal therapy.

Intervention

The intervention is non-pharmacological. Patients (donors and recipients) will be randomised to one of four groups: control (sham RIPC), late RIPC, early RIPC, or dual RIPC. Active treatment will consist of four 5-minute inflations of a blood pressure cuff on the upper arm to 40 mmHg above systolic blood pressure. The inflations will be separated by 5-minute periods when the blood pressure cuff will be deflated. To activate late phase RIPC, the inflations will occur 24 hours before surgery. Placebo treatment (sham RIPC) will consist of four 5-minute inflations of a blood pressure cuff on the upper arm to 40 mmHg.

The intervention will be applied once or twice over a 24 hour period pre-operatively. Most visits and tests (including GFR and biopsies) in the first year are part of the transplantation protocol in the centres. Data for years 2-5 will be obtained from central databases in the UK (Transplant UK) and Holland (Eurotransplant).

Outcome measures

1. GFR at 12 months after transplantation using iohexol clearance
2. estimated GFR (eGFR) at 3 months
3. Time for serum creatinine to fall by 50%
4. White cell count, CRP and plasma IL6, interferon gamma and TNF alpha before, and 1-5 days after surgery (donors and recipients)
5. Urinary IL6, interferon gamma and TNF alpha 1-5 days after surgery (recipients)
6. Kidney graft cortical tubulointerstitial fibrosis at 6 months (digital analysis of Sirius red staining in biopsy material)
7. RIPC-induced protein expressional changes in vascular and kidney tissue
8. Incidence of delayed graft function (need for dialysis in the first 7 days after transplantation or serum creatinine levels increase, remain unchanged, or decrease less than 10% per day in three consecutive days in the first week after transplantation)
9. Incidence of acute rejection during the first 12 months after transplantation
10. T cell activation, cytokine synthesis and proliferation in response to donor cells
11. Long-term outcomes using renal registry data 2-5 years after transplantation (serum creatinine/eGFR, graft survival, patient survival).

Please refer to the full protocol for details of any references mentioned in this summary. The full protocol is available on the REPAIR website http://repair.lshtm.ac.uk/ or email repair@lshtm.ac.uk to request a copy.