# Renal protection against ischaemia-reperfusion in transplantation

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| **Ethical review** | Approved WMO |
| **Status** | Recruitment stopped |
| **Health condition type** | Other condition |
| **Study type** | Interventional |

## Summary

### ID

NL-OMON32835

**Source**
ToetsingOnline

**Brief title**
REPAIR

### Condition

- Other condition

**Synonym**
Ischaemia-reperfusion injury

**Health condition**

Niertransplantatie

**Research involving**
Human

## Sponsors and support

**Primary sponsor:** University College London
**Source(s) of monetary or material Support:** NIHR en MRC

## Intervention

**Keyword:** Ischaemia, Kidney, Preconditioning, Transplantation

## Outcome measures

### Primary outcome

Glomerular filtration rate (GFR) 12 months after transplantation using iohexol clearance

### Secondary outcome

1. Time for serum creatinine to fall by 50%

2. eGFR 6 months after transplantation

3. White cell count, CRP and plasma IL6, interferon gamma and TNF alpha before, and 1-5 days after surgery (donors & recipients)

4. RIPC-induced protein expressional changes in renal tissue [analysis in biopsy material; protein kinase C (epsilon isoform; activated/membrane-bound fraction), superoxide dismutase (MnSOD), cyclo-oxygenase 2 (COX-2), inducible nitric oxide
synthase (iNOS), heat shock proteins (HSP) 27/72, reperfusion injury salvage kinases (PI3K-Akt and MEK1/2-ERK)]

5. Renal graft cortical tubulointerstitial fibrosis at 6 months (digital analysis of Sirius red staining in biopsy material)

6. Incidence of delayed graft function (serum creatinine levels increase, remain unchanged, or decrease less than 10% per day in three consecutive days

in the first week after transplantation)

7. T cell activation, cytokine synthesis and proliferation in response to donor

cells

8. Incidence of acute rejection during the first 12 months after transplantation

9. Serum creatinine and eGFR 2 to 5 years after transplantation

10. 6 month, 12 month, and 2 to 5 year patient and graft survival

# Study description

**Background summary**

The gap between the supply of kidneys for transplantation and the demand of recipients is growing steadily in the Netherlands. Between 1998 and 2008, the total number of kidney transplants has not changed significantly, despite the fact that in recent years over 50% of the patients received a kidney transplant from a living donor. Patients waiting on the transplant list endure reduced quality of life and increased death rates, not to mention the economic burden of renal replacement therapy (dialysis). Therefore, new approaches to maximise the benefit of each transplanted kidney are needed, so that each patient gets extra years of benefit. One influence on kidney function after transplantation is damage that occurs when the kidney is removed from the donor and loses its blood supply. This is known as ischaemic injury. Reconnecting the kidney to the recipient's circuation reduces ischaemic injury but triggers a second phase of injury, known as reperfusion injury. Therefore tissue damage is a combination of injury that occurs during ischaemia and reperfusion, known as ischaemia*reperfuson (IR) injury. The degree of IR injury determines the speed of recovery of kidney function in the short term and influences long term success of the transplant. Reduction in IR injury has potential to improve the outcome of kidney (and other organ) transplantation. This trial will determine whether remote ischaemic preconditioning (RIPC), an intervention that we have shown to reduce human IR injury, improves renal function after living*donor kidney transplantation.
Remote ischaemic preconditioning: Over thirty studies in animals have shown that if the blood flow to an organ is transiently cut off, this stimulates a protective reflex. This phenomenon of remote ischaemic preconditioning (RIPC) makes many different organs resistant to the damage caused by low blood flow, including the heart, lung, liver, skin and skeletal muscle. Our research group has extended these animal observations to humans and has shown that transient reductions in blood flow to the arm or leg reduces experimental IR injury in

healthy subjects and patients. Three small scale clinical trials have shown that RIPC protects the heart in children and adults undergoing heart surgery, and the kidneys in patients undergoing abdominal surgery. We have recently completed a pilot study showing that RIPC protects the kidney in living*donor kidney transplantation in children. The focus of this clinical trial is to extend these observations in a kidney transplantation trial of adequate size to measure if RIPC has protective effects that are sufficiently large to benefit patients.

## Study objective

The intervention that we will test in this trial is remote ischaemic preconditioning. Remote ischaemic preconditioning is a protective reflex that is induced by repeatedly obstructing the blood supply to the arm over a 40 minute period. We have shown this procedure reduces kidney injury in a small pilot study and now plan to do trial of sufficient size to establish the actual clinical benefit with precision.

Primary objective:
To determine if remote ischaemic preconditioning improves renal function (GFR measured by iohexol clearance) 12 months after transplantation

Secondary objective(s):
To determine the effect 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

## Study design

Double*blind, randomised, placebo-controlled
Patients (and their donors) will be will be randomised as pair to one of 4 groups:
1. sham RIPC to act as a control group
2. early phase RIPC
3. late phase RIPC
4. Dual RIPC (early and late phase RIPC)

## Intervention

Patients (donors and recipients) will be randomised to four groups: control (sham RIPC), early RIPC, late RIPC and 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 (and below systolic blood pressure).

**Study burden and risks**

1. Standard procedures for kidney transplantation will be followed in each of the centres involved in this study. This includes preoperative care, anaesthetic and surgical procedures, postoperative care and follow up thereafter.
2. The main additional procedure is the remote ischaemic preconditioning intervention. This is a benign procedure, consisting of 4 periods of inflation of a blood pressure cuff to 40 mmHg above blood pressure, each lasting for 5 minutes. Each inflation will be followed by a 5 minute period when the cuff is deflated. During the inflation of the cuff, blood flow will be cut off to the arm for 5 minutes. This will not cause any damage though there is a risk of arm discomfort. Some research subjects will undergo the preconditioning cuff inflation on two occasions, the first 24 hours before surgery and the second immediately before surgery. The kidney donor and recipient will undergo preconditioning cuff inflations. A placebo group will be included who will undergo a sham inflation of the cuff; this will be dome by inflating the cuff to a pressur of 40 mmHg and well below usual blood pressure so as not ti impede blood flow into the arm.
3. Volunteers will undergo blood and urine sampling in the first 5 days after surgery. Most of these will be as part of routine clinical care but some will be for research purposes
4. Therefore the main ethical issues will be the discomfort of the cuff inflations, preserving patient confidentiality and the inconvenience to the patients of extra blood and urine sampling. To address these issues, subjects can withdraw from the study if they do not tolerate any discomfort or inconvenience. Standard approaches to maintain patient confidentiality will be adopted whilst at the same time collecting the minimum patient*identifiable data that is needed to address the research question.
5. Tissue samples that are surplus to requirements will be collected for analyses. We will ask that these be gifted for research purposes.
6. Informed consent will be obtained from all research subjects.
7. The study will be randomised, placebo*controlled and double blind so limiting the effect of bias. The organisational issues that arise will be dealt with by the recruitment of staff to run the study at each of the sites.
8. There are no commercial conflicts of interest. The study is funded by the NIHR and the MRC.

# Contacts

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# Trial sites

## Listed location countries

Netherlands

# Eligibility criteria

**Age**
Adults (18-64 years)
Elderly (65 years and older)

## Inclusion criteria

1. Patients scheduled for living donor transplantation
2. Patients aged 18 and above

## Exclusion criteria

1. Patients with a HLA-identical kidney donor
2. Patients on ATP-sensitive potassium channel opening or blocking drugs
3. Patients on ciclosporine
4. Patients receiving a repeat transplant
5. Patients with a known iodine sensitivity (who cannot undergo iohexol clearance studies)

# Study design

## Design

| | |
|---|---|
| Study type: | Interventional |
| Intervention model: | Parallel |
| Allocation: | Randomized controlled trial |
| Masking: | Double blinded (masking used) |
| Control: | Placebo |
| Primary purpose: | Prevention |

## Recruitment

NL

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|---|---|
| Recruitment status: | Recruitment stopped |
| Start date (anticipated): | 01-12-2009 |
| Enrollment: | 100 |
| Type: | Actual |

# Ethics review

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| Approved WMO Date: | 09-11-2009 |
| Application type: | First submission |
| Review commission: | METC Leids Universitair Medisch Centrum (Leiden) |
| Approved WMO Date: | 31-10-2013 |
| Application type: | Amendment |
| Review commission: | METC Leids Universitair Medisch Centrum (Leiden) |

# Study registrations

## Followed up by the following (possibly more current) registration

No registrations found.

## Other (possibly less up-to-date) registrations in this register

No registrations found.

## In other registers

| Register | ID |
|---|---|
| ISRCTN | ISRCTN30083294 |
| CCMO | NL29832.058.09 |