Remote preconditioning for Protection Against Ischaemia–Reperfusion in renal transplantation (REPAIR): a multicentre, multinational, double-blind, factorial designed randomised controlled trial

Raymond MacAllister,¹* Tim Clayton,² Rosemary Knight,² Steven Robertson,² Jennifer Nicholas,² Madhur Motwani¹ and Kristin Veighey³

¹Division of Medicine, University College London, London, UK
²Clinical Trials Unit, London School of Hygiene and Tropical Medicine, London, UK
³Portsmouth Hospitals NHS Trust, Portsmouth, UK

*Corresponding author

Declared competing interests of authors: none

Published May 2015
DOI: 10.3310/eme02030

Scientific summary

Protection against ischaemia–reperfusion in renal transplantation

Efficacy and Mechanism Evaluation 2015; Vol. 2: No. 3
DOI: 10.3310/eme02030

NIHR Journals Library www.journalslibrary.nihr.ac.uk
Scientific summary

Background

Kidney transplantation is the best form of treatment for many patients with kidney failure. However, a shortage of donors and eventual failure of the transplant because of the effects of chronic rejection mean that many patients rely on dialysis for long-term renal replacement therapy. In comparison with having a kidney transplant, dialysis is less convenient and more expensive, and patients’ quality of life is greater when they have a functioning transplanted kidney. Extending the life of the transplanted kidney is one approach to increase the population of patients with kidney failure who are treated by transplantation. Chronic rejection is not the only determinant of the longevity of the kidney transplant. During surgery the kidney sustains ischaemic damage during the time between being disconnected from the donor’s blood supply and being reperfused on completion of the anastomosis in the recipient. A second injury occurs on reperfusion and this composite ischaemia–reperfusion (IR) injury determines the function of the transplanted kidney in the immediate postoperative period and longer term. Reducing the IR injury to the kidney will result in a healthier kidney at implantation and ultimately one that is likely to have a longer lifespan in the recipient. One approach that has been used to make organs resistant to IR injury is ischaemic preconditioning (IPC). IPC utilises sub-lethal ischaemia (preconditioning stimulus) to induce a state of protection against subsequent prolonged ischaemia, with two phases of protection. An early phase of IPC occurs within minutes of the preconditioning stimulus and lasts for up to 4 hours, whereas a late phase occurs 24 hours after the preconditioning stimulus and lasts for up to 72 hours. In animal models IPC attenuates injury and preserves function following renal IR and after renal transplantation. The logistical difficulty of applying ischaemic stimuli to induce preconditioning in vital organs in humans has precluded its clinical assessment. However, the realisation that IPC may protect tissues that are distant from those undergoing preconditioning has led to recent interest in the direct clinical application of IPC. This facet of preconditioning [termed remote ischaemic preconditioning (RIPC)] has been shown to be potentially protective against IR injury to a range of organs, including the kidney. RIPC is activated by brief non-lethal periods of ischaemia to the limb, and a number of small-scale clinical studies have demonstrated that this simple manoeuvre has protective effects in humans. The REmote preconditioning for Protection Against Ischaemia–Reperfusion in renal transplantation (REPAIR) trial sought to determine whether RIPC reduces IR injury in living-donor kidney transplantation and improves kidney function after transplantation.

Objectives

The REPAIR trial was designed to measure the effects of early and late RIPC on kidney function after living-donor transplantation. The specific research questions that were addressed were:

- Does early RIPC, late RIPC or a combination of the two improve kidney function 12 months after transplantation?
- Does RIPC have an anti-inflammatory effect?
- Which biological pathways are activated by RIPC?
- Is RIPC safe?

Methods

The REPAIR trial was a multicentre double-blind European-based randomised controlled trial assessing the impact of RIPC on kidney function following renal transplantation. Patients aged ≥ 18 years undergoing living-donor transplantation from 13 tertiary care hospitals in the UK, the Netherlands, Belgium and France were invited to take part in the study. In total, 406 pairs of transplant recipients and their living donors were recruited.
The REPAIR trial used a 2 × 2 factorial design in which the recipients and their donors were randomised to RIPC or a sham procedure both immediately before surgery (early RIPC) and 24 hours before surgery (late RIPC). Note that the terms ‘early’ and ‘late’ refer to the phase of ischaemic protection and not the timing of the intervention. Therefore, there were four arms in total:

- a sham procedure both 24 hours before and immediately pre surgery
- early RIPC and a sham procedure 24 hours before surgery
- late RIPC and a sham procedure immediately pre surgery
- early RIPC and late RIPC.

Both donor and recipient were randomised to the same intervention group. The trial intervention was a physiological procedure and was performed on both the donor and the recipient at two time points before transplantation (24 hours before surgery and immediately before surgery). The active RIPC procedure consisted of four 5-minute inflations of a blood pressure cuff on the upper arm to 40 mmHg above systolic blood pressure separated by 5-minute periods when the cuff was deflated. The sham RIPC procedure consisted of four 5-minute inflations of a blood pressure cuff on the upper arm to 40 mmHg separated by 5-minute periods when the cuff was deflated. The primary outcome was glomerular filtration rate (GFR) measured by iohexol clearance 12 months after transplantation. Secondary outcomes included estimated GFR (eGFR), systemic measures of inflammation and safety assessments.

The primary analysis was conducted on an intention-to-treat (ITT) basis, with all patients and donors, when information was available, considered in the groups to which they were randomised. A per-protocol (PP) analysis was undertaken including those who received the randomised intervention as specified [i.e. excluding those pairs in whom the intervention was not undertaken or in whom the intervention was incomplete (whether RIPC or sham)]. The primary analyses were comparisons of mean GFR at 1 year after transplantation between (1) the two arms receiving early RIPC and the two arms not receiving early RIPC and (2) the two arms receiving late RIPC and the two arms not receiving late RIPC. The model used to complete the primary analysis was a two-way analysis of covariance (ANCOVA).

**Results**

In total, 406 donor–recipient pairs were randomised: 99 to sham RIPC, 102 to early RIPC, 103 to late RIPC and 102 to dual RIPC. The PP population included 362 donor–recipient pairs.

Early RIPC resulted in a small increase in iohexol GFR (ml/minute/1.73 m²) at 12 months [58.3 vs. 55.9; adjusted difference 3.08, 95% confidence interval (CI) = –0.89 to 7.04; \( p = 0.13 \)]. There was stronger evidence for a treatment effect when eGFR was used to impute missing values (adjusted difference 3.41, 95% CI = –0.21 to 7.04; \( p = 0.065 \)) and when eGFR was used to assess kidney function (adjusted difference 4.98, 95% CI 1.13 to 8.29; \( p = 0.011 \)). The variability in the iohexol measurements was larger than anticipated, possibly because of the variability in the timing and method of measurement in the different centres. This contributed to the CIs being less precise despite the clinically important observed difference seen.

The PP analysis was consistent with this pattern; there was a small increase in iohexol GFR (ml/minute/1.73 m²) at 12 months with early RIPC (adjusted difference 3.89, 95% CI –0.18 to 7.96; \( p = 0.061 \)), an effect that was more robust when eGFR was used to impute missing values (adjusted difference 3.66, 95% CI –0.08 to 8.69; \( p = 0.055 \)) and when eGFR was used to assess kidney function (adjusted difference 4.69, 95% CI 0.69 to 8.69; \( p = 0.022 \)).

The eGFR (ml/minute/1.73 m²) was also measured at 3 months and again the pattern was similar, with an adjusted mean difference in the ITT analysis of 4.99 (95% CI 1.69 to 8.29, \( p = 0.003 \)) and in the PP analysis of 5.32 (95% CI 1.9 to 8.75, \( p = 0.002 \)).
Late RIPC had no effect on renal outcomes, with little evidence of a difference in iohexol GFR (mL/minute/1.73 m²) between those receiving late RIPC and those in the control group (adjusted difference 1.19, 95% CI –2.77 to 5.15; p = 0.56). When eGFR was used to impute the missing values of GFR measured by iohexol clearance, the adjusted mean difference was 2.18 (95% CI –1.45 to 5.8, p = 0.239), and when eGFR was used the adjusted mean difference was 1.97 (95% CI –1.87 to 5.81, p = 0.314). Analysis of the PP population was also consistent with analysis of the ITT population, with an adjusted mean difference for iohexol GFR of 1.30 (95% CI –2.76 to 5.35, p = 0.53). When eGFR was used to impute missing values of GFR measured by iohexol, the adjusted mean difference was 2.78 (95% CI –0.96 to 6.51, p = 0.145), and when eGFR was used the adjusted mean difference was 1.73 (95% CI –2.26 to 5.73, p = 0.394). Similarly, there was no difference in eGFR at 3 months between the late RIPC group and the control group, with an adjusted mean difference in the ITT population of 1.84 (95% CI –1.46 to 5.14, p = 0.273) and in the PP population of 1.59 (95% CI –1.83 to 5.01, p = 0.362). There was no evidence of an interaction between early RIPC and late RIPC for GFR and no evidence that combining early and late RIPC had additional beneficial effects on kidney function.

There was no evidence of an effect of RIPC on the short-term secondary end points. The time taken for creatinine to fall by 50% following transplantation was similar between the early RIPC group and the control group (p = 0.75) and between the late RIPC group and the control group (p = 0.64), the median time being 48 hours in all treatment groups. There was little evidence of a difference in rate of acute rejection between the early RIPC group and the control group (p = 0.86) or between the late RIPC group and the control (p = 0.17) group, but only 10% of participants experienced acute rejection during the trial. There was little evidence that the incidence of delayed graft function differed between the early RIPC group and the control group (p = 0.61) but the incidence was lower in the late RIPC group than in the control group (1.0% vs. 5.3%, p = 0.031). However, only 12 patients experienced delayed graft function and so substantial uncertainty remains over the effects of early and late RIPC on this outcome. The median length of hospital stay was 6 days in all groups. Nine recipients experienced graft loss and only two recipients died during the initial 12 months following transplant. There was little evidence of any differences between those receiving RIPC and those in the control group. The results of the PP analysis of the main secondary outcomes were similar to those of the ITT analysis.

Remote ischaemic preconditioning had no effect on the systemic inflammatory response to surgery in the donor or recipient, with similar profiles of tumour necrosis factor alpha (TNF-α), interleukin 1 beta (IL-1β), interferon gamma (INF-γ) and interleukin 6 (IL-6). RIPC was safe and well tolerated by recipients and donors.

**Conclusions**

Remote ischaemic preconditioning is a safe intervention that can be used with little added cost in living-donor transplantation. Although the evidence for an effect of RIPC on our chosen primary end point was weak, possibly because of the larger than expected variability in iohexol measurements, taken in the context of the secondary analyses (different methods of measuring the same end point) there is persuasive evidence of a clinically meaningful improvement in kidney function after transplantation.

**Trial registration**

This trial is registered as ISRCTN30083294.

**Funding**

This project was funded by the Efficacy and Mechanism Evaluation (EME) programme, a Medical Research Council and National Institute for Health Research partnership.
Efficacy and Mechanism Evaluation

This journal is a member of and subscribes to the principles of the Committee on Publication Ethics (COPE) (www.publicationethics.org).

Editorial contact: nihredit@southampton.ac.uk

The full EME archive is freely available to view online at www.journalslibrary.nihr.ac.uk/eme. Print-on-demand copies can be purchased from the report pages of the NIHR Journals Library website: www.journalslibrary.nihr.ac.uk

Criteria for inclusion in the Efficacy and Mechanism Evaluation journal
Reports are published in Efficacy and Mechanism Evaluation (EME) if (1) they have resulted from work for the EME programme, and (2) they are of a sufficiently high scientific quality as assessed by the reviewers and editors.

EME programme
The Efficacy and Mechanism Evaluation (EME) programme was set up in 2008 as part of the National Institute for Health Research (NIHR) and the Medical Research Council (MRC) coordinated strategy for clinical trials. The EME programme is broadly aimed at supporting ‘science driven’ studies with an expectation of substantial health gain and aims to support excellent clinical science with an ultimate view to improving health or patient care.

Its remit includes evaluations of new treatments, including therapeutics (small molecule and biologic), psychological interventions, public health, diagnostics and medical devices. Treatments or interventions intended to prevent disease are also included.

The EME programme supports laboratory based or similar studies that are embedded within the main study if relevant to the remit of the EME programme. Studies that use validated surrogate markers as indicators of health outcome are also considered.

For more information about the EME programme please visit the website: http://www.nets.nihr.ac.uk/programmes/eme

This report
The research reported in this issue of the journal was funded by the EME programme as project number 08/52/02. The contractual start date was in July 2009. The final report began editorial review in August 2014 and was accepted for publication in January 2015. The authors have been wholly responsible for all data collection, analysis and interpretation, and for writing up their work. The EME editors and production house have tried to ensure the accuracy of the authors’ report and would like to thank the reviewers for their constructive comments on the final report document. However, they do not accept liability for damages or losses arising from material published in this report.

This report presents independent research. The views and opinions expressed by authors in this publication are those of the authors and do not necessarily reflect those of the NHS, the NIHR, the MRC, NETSCC, the EME programme or the Department of Health. If there are verbatim quotations included in this publication the views and opinions expressed by the interviewees are those of the interviewees and do not necessarily reflect those of the authors, those of the NHS, the NIHR, NETSCC, the EME programme or the Department of Health.

© Queen’s Printer and Controller of HMSO 2015. This work was produced by MacAllister et al. under the terms of a commissioning contract issued by the Secretary of State for Health. This issue may be freely reproduced for the purposes of private research and study and extracts (or indeed, the full report) may be included in professional journals provided that suitable acknowledgement is made and the reproduction is not associated with any form of advertising. Applications for commercial reproduction should be addressed to: NIHR Journals Library, National Institute for Health Research, Evaluation, Trials and Studies Coordinating Centre, Alpha House, University of Southampton Science Park, Southampton SO16 7NS, UK.

Published by the NIHR Journals Library (www.journalslibrary.nihr.ac.uk), produced by Prepress Projects Ltd, Perth, Scotland (www.prepress-projects.co.uk).
Efficacy and Mechanism Evaluation  Editor-in-Chief

Professor Raj Thakker  May Professor of Medicine, Nuffield Department of Medicine, University of Oxford, UK

NIHR Journals Library Editor-in-Chief

Professor Tom Walley  Director, NIHR Evaluation, Trials and Studies and Director of the HTA Programme, UK

NIHR Journals Library Editors

Professor Ken Stein  Chair of HTA Editorial Board and Professor of Public Health, University of Exeter Medical School, UK

Professor Andree Le May  Chair of NIHR Journals Library Editorial Group (EME, HS&DR, PGfAR, PHR journals)

Dr Martin Ashton-Key  Consultant in Public Health Medicine/Consultant Advisor, NETSCC, UK

Professor Matthias Beck  Chair in Public Sector Management and Subject Leader (Management Group), Queen's University Management School, Queen's University Belfast, UK

Professor Aileen Clarke  Professor of Public Health and Health Services Research, Warwick Medical School, University of Warwick, UK

Dr Tessa Crilly  Director, Crystal Blue Consulting Ltd, UK

Dr Peter Davidson  Director of NETSCC, HTA, UK

Ms Tara Lamont  Scientific Advisor, NETSCC, UK

Professor Elaine McColl  Director, Newcastle Clinical Trials Unit, Institute of Health and Society, Newcastle University, UK

Professor William McGuire  Professor of Child Health, Hull York Medical School, University of York, UK

Professor Geoffrey Meads  Professor of Health Sciences Research, Faculty of Education, University of Winchester, UK

Professor John Powell  Consultant Clinical Adviser, National Institute for Health and Care Excellence (NICE), UK

Professor James Raftery  Professor of Health Technology Assessment, Wessex Institute, Faculty of Medicine, University of Southampton, UK

Dr Rob Riemsma  Reviews Manager, Kleijnen Systematic Reviews Ltd, UK

Professor Helen Roberts  Professor of Child Health Research, UCL Institute of Child Health, UK

Professor Helen Snooks  Professor of Health Services Research, Institute of Life Science, College of Medicine, Swansea University, UK

Please visit the website for a list of members of the NIHR Journals Library Board: www.journalslibrary.nihr.ac.uk/about/editors

Editorial contact: nihredit@southampton.ac.uk