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

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Scientific summary

Protection against ischaemia–reperfusion in renal transplantation

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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 m^2) 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 m^2) 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 m^2) 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 m^2) 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.

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