Remote Ischemic Preconditioning Does Not Affect the Incidence of Acute Kidney Injury After Elective Abdominal Aortic Aneurysm Repair

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Objective: **Open abdominal aortic aneurysm (AAA) repair is associated with a high risk of renal injury with few known strategies demonstrating a reduction in this risk. Remote ischemic preconditioning (RIPC) has been identified as having the potential to minimize organ injury following major vascular surgery. This trial investigated the potential for RIPC to attenuate renal and myocardial injury in patients undergoing elective open AAA repair.**

Design: **Prospective, randomized double-blinded control trial.**

Setting: **Tertiary referral hospital.**

Participants: **Sixty-two patients undergoing elective open AAA repair.**

Intervention: **RIPC was achieved via three 5-minute cycles of upper limb ischemia using a blood pressure cuff or control (sham cuff).**

Measurements: **Primary outcome was the occurrence of renal injury, as measured by an increase in creatinine during the first 4 postoperative days. Secondary outcomes included urinary neutrophil-gelatinase-associated lipocalin (NGAL), occurrence of acute kidney injury (AKI), occurrence of myocardial injury as defined by troponin rise, incidence of postoperative complications, and mortality.**

There was no difference in postoperative creatinine levels, NGAL levels, or the occurrence of AKI between the groups at any postoperative time point. Similarly, there was no difference in the occurrence of myocardial injury or mortality. Of note, 6 patients in the RIPC group, while no patient in the control group, experienced postoperative complications that required repeat surgical laparotomy, potentially masking any renoprotective effects of RIPC.

Conclusion: **RIPC did not reduce the risk of postoperative renal failure or myocardial injury in patients undergoing open AAA repair. The authors' results do not support the introduction of this technique to routine clinical practice.**

KEY WORDS: remote ischemic preconditioning, acute kidney injury, vascular surgery, aortic aneurysm

RENAL INJURY is an important cause of morbidity and mortality following abdominal aortic aneurysm (AAA) repair.[1,2] Development of acute renal failure (ARF) is multifactorial. Risk factors include pre-existing renal impairment, aortic cross-clamping, and ischemia–reperfusion injury after clamp release. ARF develops in up to 10% of patients after elective open AAA repair and is an independent predictor of death.[1,3] To date, there is no robust evidence that existing pharmacologic or other interventions used to protect the kidneys during vascular surgery are beneficial.[4] Additionally, cardiac events represent a significant cause of perioperative morbidity and mortality in patients undergoing AAA surgery.[1,5] Subclinical myocardial injury after major vascular surgery, detected by a rise in cardiac troponin, occurs in up to 30% of patients and is associated with increased mortality.[6–11] There remains, therefore, a need to identify renoprotective and cardioproctective strategies during the perioperative period in these high-risk patients.

Remote ischemic preconditioning (RIPC) has been shown in some studies to improve renal and cardiac indices following major cardiac or vascular surgery.[12–18] In remote ischemic preconditioning, a series of short periods of ischemia followed by periods of reperfusion render organs more resistant against subsequent ischemic events. The mechanism for RIPC has not been elucidated; however, signalling between tissues and organs probably occurs via humoral and neural pathways[19,20] Originally, preconditioning was discovered by applying ischemic stimuli directly to the organ to which the protection was being targeted; however, more recently, distant organs have been used for preconditioning; in particular, skeletal muscle.

The ease by which remote ischemic preconditioning (RIPC) may be performed makes it an attractive technique to protect against systemic organ injury in patients undergoing vascular surgery. Therefore, the authors hypothesized that the application of RIPC to the upper limb would attenuate increases in serum creatinine after open abdominal aortic aneurysm repair.

METHODS

This prospective, randomized, double-blind, single-center study was approved by the institutional research ethics committee, and written informed consent was obtained from all patients (Trial registration: ISRCTN11019960).

Adult patients undergoing primary elective AAA repair were invited to participate in this study at the time of hospital admission between September 2009 and December 2012. Exclusion criteria included refusal of consent, myocardial infarction in the preceding two weeks, history of upper limb vascular insufficiency, and emergency AAA repair. Those patients with kidney disease requiring renal replacement therapy also were excluded.

Anesthesia was induced by 1 of 3 senior vascular anesthesiologists with propofol, fentanyl, and rocuronium, and the trachea was intubated and the patient ventilated. Maintenance of anesthesia was with sevoflurane. Prophylactic antibiotics were administered, and normothermia was maintained using a convective air system. All patients received systemic heparin anticoagulation (75 u/kg) prior to aortic cross-clamp. Standard monitoring included continuous

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electrocardiography and continuous recording of heart rate, arterial blood pressure, central venous pressure, pulse oximetry, end-tidal carbon dioxide concentration, and body temperature. One of 3 attending vascular surgeons conducted the operative procedure. Perioperative pain management of epidural analgesia, intrathecal opiates, continuous wound infusion catheter, or patient-controlled analgesia (PCA) was at the discretion of the individual attending anesthesiologist. Care was provided for patients in a dedicated vascular surgical high-dependency unit (HDU) for at least 48 hours postoperatively.

On the morning of surgery, patients were assigned randomly, using a random number generator in a 1:1 ratio for parallel arms and using a concealed allocation approach (computer-generated codes, Microsoft Excel, Microsoft Corporation, Seattle, WA) with sealed envelopes to (1) the RIPC group or (2) the control group. Study investigators, attending anesthesiologists, and surgical staff were blinded to treatment assignments. This was achieved by a third party placing the cuff on the patient's upper arm in the RIPC group or on a bag of saline concealed under surgical drapes in the control group.

The RIPC protocol was commenced postinduction of anesthesia and after placement of a central venous line and completed prior to the application of the aortic cross-clamp. The RIPC protocol consisted of 3 cycles of upper arm ischemia. Each cycle was induced by a blood pressure cuff inflated to 100 mmHg above systolic blood pressure for 5 minutes, followed by deflation for a period of 5 minutes (reperfusion period).[13,14]

The primary outcome measure was renal injury defined by an increase in serum creatinine levels during the first 4 days following open AAA repair. Secondary outcome measures included urinary NGAL (NGAL Test™ Reagent Kit [ST001CA], Bioporto Diagnostics), urea, urine output, presence of acute kidney injury (using AKIN criteria and NGAL), myocardial infarction (MI), myocardial injury (as measured by troponin), length of hospital stay, and death. Post hoc analysis examined the occurrence of major adverse outcomes.

AKIN criteria were calculated daily for each patient (stage I, II or III)[21]; AKI was defined as an abrupt (within 48 hours) increase in s-creatinine >26.5 μmol/L (0.3 mg/dL) or a relative increase in s-creatinine >50%, or a decrease in urine output to less than 0.5 mL/kg/h for more than 6 hours. Myocardial infarction was defined as a troponin rise to greater than the upper limit of normal for the test conducted, with at least 1 of the following: Typical symptoms of ischemia, ST/T wave changes, or left bundle-branch block, new pathologic Q-waves, imaging evidence of new loss of viable myocardium or regional wall motion abnormality or identification of a new intracoronary thrombus according to the American College of Cardiology/American Heart Association guidelines. During the study period, the hospital laboratory changed from measuring troponin I (E 170, Roche Diagnostics, Mannheim, Germany) to troponin T (high sensitivity) (E170, Roche Diagnostics, Mannheim, Germany). Therefore, troponin concentrations were not compared directly between groups; the detection of a troponin level (either subunit) above the upper limit of normal, using the hospital laboratories standard reference range, was classified as troponin positive for that day. The number of troponin-positive patients between groups was then compared.

Blood and urine specimens were taken preoperatively, 4 hours following extubation and on the morning of postoperative days 1 to 3 inclusive. Each morning after surgery until postoperative day 3, 12-lead ECGs were performed.

The sample size was calculated to detect a 25% difference in peak postoperative creatinine levels. Suitable data for postoperative creatinine, following open AAA repair, were not available in the literature at the time of study design. Therefore, from January to August 2009, the authors recorded all creatinine values at baseline, and for the first 4 postoperative days in patients who had undergone open AAA repair in their institution (N = 16). Peak creatinine level occurred on day 2 postoperatively (105.94 +/- 44.7 μmol/L). Based on this data, to detect a 25% reduction in peak postoperative creatinine, a total of 25 patients per group were required (alpha and beta of 0.05 and 0.2, respectively). Given that test creatinine values were distributed abnormally, the number of subjects was increased by 20% to compensate for the reduced power of nonparametric statistical tests to detect significant differences. Therefore, it was planned to recruit a total of 31 patients in each group. All power calculations were performed using GraphPad Statmate 2.00, Graphpad Software Inc, La Jolla, CA). Data were analyzed on an intention-to-treat basis. Descriptive variables are presented as medians and interquartile ranges. Categorical data are expressed as frequency and percentage and compared with Chi squared, Fisher's exact test, or the Cochran-Armitage test for trend where appropriate. Multiple comparisons between groups were performed using the Kruskal-Wallis test or repeat measures ANOVA. Normality of data was tested using the D'Agostino-Pearson normality test. Conventional levels of significance (0.05) were applied throughout. A posthoc analysis of the data was undertaken to exclude patients who returned to the operating room within 3 days of the original surgery. Statistical analysis was undertaken using Prism 6 (Graphpad Software, La Jolla, CA).

RESULTS

Between September 2009 and December 2012, all patients referred for elective open AAA repair at St Vincent's University Hospital (Dublin, Ireland) were invited to participate in this trial. Two patients declined invitation and a further two patients were excluded (upper limb vascular insufficiency, leaking AAA with hemodynamic instability). In total, 62 patients presenting for open AAA repair were included in this study; 31 patients were randomized to the RIPC group, and 31 patients were randomized to the control group (conventional open AAA repair) (Fig 1). All patients received the intended treatment, completed the study protocol, and were included in the analysis.

Baseline characteristics (Table 1) and operative characteristics (Table 2) were similar between groups. There were no significant differences with regard to aortic cross-clamp time, site of cross-clamp application, or graft type.

Serum creatinine levels increased from baseline during the first 48 hours postoperatively, returning to their preoperative values by day 3 (Fig 2). The greatest increase occurred at postoperative day 1 in both groups. There was no significant difference between creatinine values in the RIPC or control group at any time point (Table 3). Urinary NGAL levels increased as early as 4 hours postoperatively, with peak values occurring at day 3 (Fig 2), with no significant difference in urinary NGAL concentration at any time point between groups (Table 3). Similarly, no significant differences in urea or urine output were detectable at any time point between the RIPC group and control group (Table 4).

A total of 28 patients (45%) were diagnosed with AKI according to the AKIN criteria at any time point, 11 patients (35%) in the control group and 17 patients (54%) in the RIPC group. However, this difference was not statistically significant (0.12) (Table 3). When NGAL levels (using an NGAL cut-off of >250 ng/L, as per manufacturer's recommendations[22]) were used to define clinically relevant renal injury, AKI occurred in 22 patients (36%), nine patients (29%) in the control group and 13 (42%) in the RIPC group (Table 3).

Twenty-five (40%) of the 62 patients had a new troponin rise postoperatively, (16 in the RIPC group and 9 in the control group (p = 0.11); RIPC was not associated with a reduction in the number of patients with a troponin increase above the upper limit