Remote Ischemic Preconditioning in High-risk Cardiovascular Surgery Patients: A Randomized-controlled Trial

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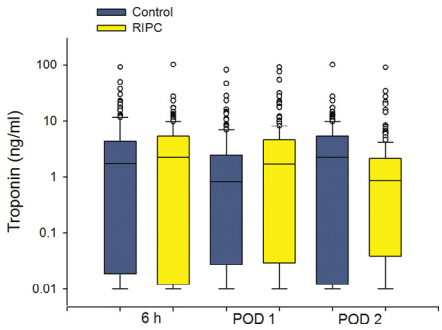
Remote ischemic preconditioning (RIPC) may reduce biomarkers of ischemic injury after cardiovascular surgery. However, it is unclear whether RIPC has a positive impact on clinical outcomes. We performed a blinded, randomized controlled trial to determine if RIPC resulted in fewer adverse clinical outcomes after cardiac or vascular surgery. The intervention consisted of 3 cycles of RIPC on the upper limb for 5 minutes alternated with 5 minutes of rest. A sham intervention was performed on the control group. Patients were recruited who were undergoing (1) high-risk cardiac or vascular surgery or (2) cardiac or vascular surgery and were at high risk of ischemic complications. The primary end point was a composite outcome of mortality, myocardial infarction, stroke, renal failure, respiratory failure, and low cardiac output syndrome, and the secondary end points included the individual outcome parameters that made up this score, as well as troponin-I values. A total of 436 patients were randomized and analysis was performed on 215 patients in the control group and on 213 patients in the RIPC group. There were no differences in the composite outcome between the 2 groups (RIPC: 67 [32%] and control: 72 [34%], relative risk [0.94 {0.72-1.24}]) or in any of the individual components that made up the composite outcome. Additionally, we did not observe any differences between the groups in troponin-I values, the length of intensive care unit stay, or the total hospital stay. RIPC did not have a beneficial effect on clinical outcomes in patients who had cardiovascular surgery.

Semin Thoracic Surg ■■:■■–■■

Keywords: remote ischemic preconditioning, cardiovascular surgery, ischemia-reperfusion



Troponin-I values 6 hours after vascular surgery and on postoperative days 1 and 2.

Central Message

The application of remote ischemic preconditioning before high-risk vascular or cardiac surgery did not improve clinical outcomes as assessed with a composite end point measure.

Perspective Statement

Previously, remote ischemic preconditioning (RIPC) was associated with improvements in cardiac biomarkers, but it was unclear how these findings would translate to clinical outcomes. We investigated whether RIPC was associated with improved outcomes after high-risk cardiac or vascular surgery. We did not find a difference between RIPC and the control intervention. RIPC does not confer any benefit during high-risk cardiovascular surgery.

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This study was funded by the Southeastern Ontario Academic Medical Organization's Innovation Fund.

The authors report no conflicts of interest. Funding was provided by the Southeastern Ontario Academic and Medical Organization.

Clinical trial registration: ClinicalTrials.gov: NCT01328912.

Research Ethics Board approval: Queen's University and Affiliated Teaching Hospitals #6005871, initial approval on June 8, 2011.

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INTRODUCTION

Cardiovascular surgical interventions are among the most common surgical procedures performed worldwide. These procedures are associated with a predictable array of adverse events. Perioperative complications of cardiac and vascular surgery include myocardial infarction (MI), stroke, renal failure, and death.[1-5] With an aging patient population and an increasing number and degree of concomitant comorbid conditions, the risk associated with these procedures increases proportionally. Adverse events associated with cardiovascular surgical procedures can have dramatic consequences on patients and families, including pain, prolonged

1043-0679/$-see front matter

https://doi.org/10.1053/j.semtcvs.2017.09.001

hospitalization, permanent disabilities, and loss of independence. The already overburdened health-care system suffers as well, with increased attendant costs. Thus, there is an appropriate interest in interventions that may mitigate these risks.

During cardiac and vascular surgery, restoration of blood flow after bypass or clamping can induce ischemia-reperfusion injury that is defined as the death of cells not due to the ischemia itself.[6,7] Remote ischemic preconditioning (RIPC) refers to the application of transient periods of reduced or absent blood supply to a distant tissue bed that is subsequently reperfused. The idea is that the initial ischemic insult will confer some degree of protection from a secondary ischemic insult.[8] Over the last decade, this idea has transitioned from animal to human models, and the ischemic preconditioning is performed at a remote tissue bed (such as an arm or a leg) with the goal of inducing a protective response in target tissues and organs (such as the heart, kidneys, or brain). Although the underlying mechanism of the purported benefits of RIPC remains unclear, it has been proposed that humeral and neural signals transmitted from remote tissues impact intracellular signaling and mitochondrial functioning within target tissues, decreasing proinflammatory gene expression and function.[9]

Initial human studies of RIPC have shown promise as surrogate biomarkers of end organ damage are reduced during various surgical interventions.[10-12] However, how such findings would translate to clinical outcomes is unclear. Recently, 2 multicenter randomized control trials examining outcomes after cardiac surgery have found no benefit of RIPC.[13,14] In addition, a pilot trial examining clinical end points after vascular surgery has found no difference between RIPC and control groups.[15] Previous studies have examined the impact of RIPC in high-risk cohorts, where risk was assessed based on the European System for Cardiac Operative Risk Evaluation (EuroSCORE).[13,16] However, surgical risk assessment tools have inherent limitations, and it has been recognized that true risk assessment can be overestimated, possibly in some types of surgery more than others.[17] We chose to examine patients deemed to be at high clinical risk, as judged by having a high-risk surgery, having a repeat surgery, or those who had substantial surgical risk factors. Considering their increased risk of ischemic complications, this cohort could potentially realize important benefits from any protective effect incurred by RIPC. We hypothesized that RIPC would improve clinical outcomes in a cohort of high-risk vascular and cardiac surgical patients.

METHODS

This trial (NCT01328912) was approved by the Queen's University Health Sciences and Affiliated Hospitals Research Ethics Board. All participants provided informed consent.

Participants

Eligible participants were adults over the age of 18 who were undergoing either (1) cardiac or vascular surgical procedures and were at increased risk of suffering ischemia-related events, (2) preoperative screening indicating cardiovascular disease, or (3) undergoing higher-risk surgery. We considered there to be an increased risk of ischemia-related events there was preoperative evidence of prior MI, unstable angina, an ejection fraction less than 40%, a prior stroke or transient ischemic attack, chronic renal insufficiency (estimated glomerular filtration rate less than 60 mL/min), or limb claudication. Preoperative screening indicating cardiovascular disease included a positive MIBI scan or an angiogram, a cardiac computed tomography, or a magnetic resonance imaging with evidence of 1 or more coronary arteries with greater than 70% stenosis, or a carotid Doppler ultrasound showing greater than 70% stenosis, uni- or bilaterally. High-risk surgery was defined as a combined valve-coronary artery bypass graft (CABG) surgery, double valve surgery, aortic surgery, left ventricle aneurysm repair, redo surgery, or open abdominal or thoracoabdominal aneurysm repair. Participants underwent follow-up assessments at 30 days, which were performed mainly by telephone interview.

Intervention

This was a single-center study and the participants were randomized in a 1:1 ratio to receive the RIPC or a sham RIPC treatment (control) by a biostatistician. Randomization was done with a computer-generated scheme and opaque sealed envelopes. The patients were enrolled and assigned to intervention by a research nurse. Surgeons, anesthetists, and postoperative care providers were blind to the group assignments, and the patients were instructed not to disclose whether they had received the intervention.

The intervention was initially planned to occur once the patient was inside the operating room (OR) under anesthesia. The protocol was modified such that the RIPC intervention occurred immediately before the patient was transferred to the OR. This change was made due to time constraints within the OR as well as difficulty and restrictions of line placement (arterial lines or intravenous lines) that were not available for use and threatened blinding with a blood pressure cuff cycling. The intervention was well tolerated and no significant complaints were voiced by the patients. Patients were transferred to the OR immediately following the completion of the RIPC intervention, where access and monitoring lines were placed and the operation commenced. The window of protection provided by RIPC was postulated to be approximately 2 hours[18]; therefore, we were well within this time frame. A blood pressure cuff was placed on the patient's upper arm. The RIPC stimulus consisted of 3 cycles of 5 minutes of ischemia with the cuff inflated to 200 mm Hg alternated with 5 minutes of cessation of pressure. The intervention occurred in isolation with only the research nurse and the patient present, to ensure all OR staff and caregivers remained blinded. The control group received similar treatment, in terms of blood pressure cuff application and segregation, although the cuff was not inflated. All patients were instructed not to disclose whether they had received the intervention.

Procedures

The anesthetic protocol was performed as per the standard practices of the attending anesthetist. In general, anesthesia was induced with intravenous midazolam, opiate (fentanyl or sufentanil), propofol or etomidate, and rocuronium. Anesthesia was maintained with desflurane, sevoflurane, or propofol infusion with opiate and