Remote Ischemic Conditioning (RIC) to Decrease Postoperative Complications After Major Abdominal Surgery - A Phase IIa Trial

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I. STUDY TITLE: Remote Ischemic Conditioning (RIC) to Decrease Postoperative Complications After Major Abdominal Surgery - A Phase IIa Trial

II: STUDY GOALS AND OBJECTIVES:

1. To obtain preliminary data regarding postoperative complications in subjects undergoing abdominal surgery and receiving remote limb ischemic or sham conditioning.

Subjects undergoing abdominal surgery will be prospectively randomized in equal proportions to receive either remote or sham lower limb ischemic conditioning immediately before surgery commences and on postoperative days 1 and 2. Each intervention will comprise 3 cycles of 5/5 minutes of inflation/deflation of a pneumatic cuff on mid-thigh. Postoperative complications within 30 days after surgery will be evaluated using Comprehensive Complication Index (CCI)[1], a continuous, scaled (0-100) and a validated measure of the total complications burden.

The preliminary data is expected to help in determining whether larger trials of RIC to decrease postoperative complications should be pursued, and provide more reliable estimates of CCI without and with RIC, sample sizes and power in design of larger trials.

2. To test whether remote limb ischemic conditioning (RIC) decreases systemic inflammatory response in patients undergoing major abdominal surgery.

Time-dependent differences between the two groups in plasma levels of inflammatory cytokines (TNF-a, IL - 1β, 6, 8 and 10), acute phase proteins (C reactive protein [CRP], alpha-1-acid glycoprotein, fibrinogen [FGN], and haptoglobin) complement components (C2, C4b, C5, C5a, and C5b-9), and blood leukocyte gene expression at baseline and one hour after completion of surgery and the second and third interventions will be tested for significance. It is hypothesized that RIC would decrease systemic inflammatory response to major surgery.

III: BACKGROUND:

Major abdominal surgery is associated with a high risk of post-operative complications. Up to 16.4% of all general surgery patients may have at least one complication. This proportion increases with the complexity of the surgery.[2] More severe complications are associated with death and longer hospital stay.[2] One of the common pathways contributory to an increase in complications is excessive systemic inflammation in response to the stress of surgery. In one study, plasma levels of C-reactive protein (CRP), an acute-phase reactant and marker of inflammation, as well as interleukin (IL) 6 (a known pro-inflammatory cytokine), were increased in trauma patients with multi-organ dysfunction syndrome (MODS) compared to those without organ dysfunction.[3] By contrast, levels of IL-10, an anti-inflammatory cytokine, were decreased in patients with MODS.[3] Another study confirmed these findings in major abdominal surgery; plasma levels of pro-inflammatory cytokines IL-6 and IL-8 were increased, although levels of the

anti-inflammatory cytokine IL-10 were also increased.[4] This study and another by the same group also showed activation of the complement cascade with surgery, both via the classical and alternate pathways.[4,5] Thus, major abdominal surgery induces significant changes in the innate immune system, changes that may be excessive and may contribute to complications after surgery in some patients.

Remote ischemic conditioning (RIC) is an innate biological phenomenon wherein a brief ischemic stimulus in an organ or tissue such as skeletal muscle induces protection in remote/distant organs against ischemia and other noxious stimuli. This effect can be induced by repeated and intermittent inflation of a pneumatic tourniquet or a blood pressure cuff on a leg or arm for 5-10 minutes for 3 or 4 times to a pressure adequate to occlude arterial flow interspersed with deflation of 5 minutes. RIC has been applied in many contexts in animal models. In rabbits, femoral artery occlusion-induced ischemia was shown to be protective against myocardial infarction following coronary occlusion.[6] In a mouse model of resuscitation from hemorrhagic shock, RIC prevented liver and lung injury; this study showed that ischemic conditioning was beneficial when applied before or after the induction of shock. However, the protective effect from postconditioning was less than that from preconditioning.[7] Other groups have shown in healthy volunteers that RIC induces anti-inflammatory effects, including modulation of blood leukocyte gene expression,[8] decrease in complement C3 expression,[9] and a decrease in overall inflammation by multiple other pathways.[10]

Translation of RIC to clinical practice has been met with mixed success. Intra-operative RIC induced via 10-minute cycles of iliac artery clamping was shown to provide myocardial and renal protection in patients undergoing open repair of abdominal aortic aneurysm.[11] RIC applied daily over a long period of time may be beneficial in reducing the rate of strokes in patients with intracranial arterial stenosis.[12] Finally, preoperative RIC was shown to decrease acute kidney injury (AKI) in subjects undergoing major cardiac surgery.[13] However, in two larger trials in cardiac surgery, RIC failed to show any differences in several clinical outcomes.[14,15] It is possible that the use of propofol may have blunted the effect of RIC in these latter studies. Thus, the role of RIC in surgical patients is unclear. It is noteworthy that in most of the trials in surgical patients the RIC stimulus was applied only preoperatively.

Recently, this group of investigators commenced an evaluation of remote ischemic conditioning in combined pre and postoperative settings. It is based on the premise that ischemic preconditioning only, especially when applied only once and immediately before commencement of surgery, may not induce a strong enough biological protective response. Furthermore, it is postulated that a combination of pre-and postconditioning extending into the postoperative period is more likely to provide a stronger beneficial effects. Recently, the investigators completed a pilot study to examine feasibility and tolerance of lower limb

ischemic conditioning pre and postoperatively (a total of five applications) in liver transplant recipients. A majority of patients tolerated all four postoperative interventions. The current study aims to apply the RIC stimulus in patients undergoing major abdominal surgery, and test whether RIC decreases inflammatory response following major abdominal surgery.

IV. STUDY HYPOTHESIS:

The central hypothesis of the research is that pre- and post-operative RIC in patients undergoing major abdominal surgery would decrease the systemic inflammatory response to major abdominal surgery and decrease postoperative complications.

V. STUDY DESIGN:

A prospective, randomized, double – masked clinical trial of RIC will be conducted in adult patients undergoing major abdominal surgery at University Hospital (UH) in Newark, NJ. Participants will be randomized into two groups: RIC and No RIC. In the RIC group, RIC will be induced at three time points – the first after anesthesia induction but before commencement of surgery, and the second and the third on post-operative days 1 and 2, respectively. The RIC intervention consists of 5 minutes of inflation of a pneumatic tourniquet placed mid-thigh followed by 5 minutes of deflation, repeated for 3 cycles. The pressure used will be 250 mmHg for the pre-operative intervention (a high pressure chosen because of significant variability of patient blood pressures in a recently anesthetized patient). Tourniquet pressures in postoperative interventions will be 50 mmHg above the patient's systolic blood pressure (the blood pressure is expected to be less labile than immediately after anesthesia induction). The No RIC group will receive a sham intervention at time points identical to those in the RIC group. The thigh tourniquet will be inflated to only 20 mmHg (to mask the intervention from the subject). Persistence of arterial flow will be confirmed with Doppler interrogation.

VI. STUDY POPULATION:

Adults ($\geq$ 18 years of age) of both sexes scheduled for elective major abdominal surgery at UH are eligible for inclusion. Major abdominal surgery is defined as surgery expected to last $\geq$ 120 minutes (from incision to closure) with an expected hospital stay $\geq$ 2 days. A list of surgeries considered for inclusion is included as Appendix A. Additional operations will be considered for inclusion if the study team and primary surgical team both agree that the procedure is a major abdominal surgery and that the duration of surgery is likely to be $\geq$ 2 hours.

Inclusion criteria

1. Adults ($\geq$ 18 years of age)
2. Both genders

3. Undergoing major abdominal surgery as above
4. Elective surgeries
5. Both outpatients and in-hospital patients
6. Post-op length of stay expected to be at least 2 days by the primary surgical service

Exclusion Criteria

1. Subjects with lower extremity paralysis
2. Lower extremity amputees
3. Known, documented peripheral arterial disease
4. Body mass index $\geq$ 45
5. Pregnancy
6. Trauma patients
7. Organ transplant recipients
8. Prior major surgery during current hospitalization (for instance, a patient undergoing re-laparotomy for a complication from a previous procedure)
9. Patient taking sulfonylureas or nitrates prior to or during admission (listed in Appendix B)
    a. These subjects are excluded because sulfonylureas are shown to abrogate the RIC effect whereas nitrates are shown to mimic the RIC effect in animal models.
10. Non-elective surgeries (urgent or emergent surgeries)
11. General surgical procedures with no planned intra-abdominal component

VII. RESEARCH METHODS:

VII.1 Recruitment and enrollment: Eligible candidates for participation will be identified by communication with the general surgery house staff and attendings. Outpatients and inpatients at University Hospital in Newark, NJ will be screened. Outpatients will be approached for study participation either in the outpatient office or in UH on the morning of surgery. Inpatients will be approached for study participation, either the day before or on the morning of the surgery.

VII.2 Randomization: Eligible and consenting subjects will be enrolled and randomized. A randomization table was created using a table of random numbers to assign subjects to RIPC and No RIPC groups. Subjects will be randomized in blocks of 6 to ensure equal randomization into the two groups. The randomization table has been entered into the REDCAPs program. After enrollment, the research team member who will conduct the intervention will access the REDCAPS program online immediately before the induction of anesthesia and obtain group assignment.

VII.3 Masking: The study will be conducted in a double-masked fashion. Investigative team member/s that will carry out randomization and administer the intervention will not be involved in evaluation of clinical and laboratory outcomes. The primary surgical team, nurses, and any consulting services caring for the patient will be unaware of the group assignment. Other care providers will not be informed of the group assignment. Outcome assessors will not be involved in randomization and administration of the RIC intervention. Adequate steps are in place to mask the outcome assessors (clinical and laboratory) from knowing group assignment.

Subjects will be masked from recognizing which group they are in in the following manner: a) Subjects will not be informed of the group assignment throughout their participation in the study; b) subjects randomized to No RIPC will have a tourniquet placed on the thigh and inflated. It is anticipated that the subject is likely to perceive the inflation as the true RIPC. No information will be provided to subjects regarding the amount of pressure used to inflate the tourniquet in either group.

VII.4 RIC Intervention and Perioperative Care: Sham and RIC interventions will be as described above in section V. All other aspects of anesthesia care will be as per standards of practice. All aspects of the surgical procedure and postoperative care including decisions regarding discharge will be as per standards of practice. The diagnosis and treatment of complications will be under the purview of the clinical care team. The research team will not participate in the clinical care of the subjects.

VII.5 Blood Sample Collection and Processing: Ten mL of venous blood (10mL) will be collected at baseline, an hour after completion of skin closure, and an hour after completion of second and third RIC interventions. 2.5 mL will be placed in PAXgene Blood RNA tubes (Qiagen) for RNA isolation from leukocytes. RNA will be submitted to our Molecular Resource Facility for RNA sequencing. Remaining blood will be placed in EDTA tubes, centrifuged at 3500 rpm and plasma will be stored in aliquots at -70^{0}C.

VIII. Outcomes:

VIII.1 Primary Outcome:

The CCI, a validated and scaled score of all surgical complications (range 0 [no complications] to 100 [death]) is the primary outcome.

All complications within 30 days after surgery will be graded as per Clavien-Dindo classification.[1,2] CCI will be computed for each subject using the publically available website, http://www.assessurgery.com/. Follow up after discharge will occur either in clinic or via telephone

VIII.2 Secondary Clinical Outcomes:

1. Proportion of patients in each group that complete all three RIC interventions
2. Hospital days

3. 30-day mortality (will be captured as part of CCI)

VIII.3 Secondary Molecular Outcomes:

1. Plasma cytokines levels (TNF-a, IL - 1β, 6, 8 and 10)
2. Plasma acute phase reactant proteins (CRP, alpha-1- acid glycoprotein, FGN, and haptoglobin)
3. Plasma complement levels (C2, C4b, C5, C5a, and C5b-9)
4. Peripheral blood leukocyte gene expression profiles determined by RNA sequencing.

Commercially available kits will be used for the plasma assays in section VIII.3.

IX. Data Collection and Analysis:

IX.1 Data Collection, and Study Variables

Data regarding subject screening for eligibility, recruitment, and enrollment will be stored in an Excel file on a dedicated Rutgers server with password protection. Other data will be entered electronically into case report forms via the online REDCaps software. Hard copy case report forms are also available as needed to facilitate the transfer of data to online software.

IX.2 Case Report Forms (CRFs)

5 CRFs will be used to collect study-related data as follows.

- CRF 1 will capture baseline characteristics. Variables collected will include age, sex, ethnicity, height, weight, baseline medical characteristics, length of hospital stay, baseline laboratory values, and care needs at the time of surgery (whether hospitalized, in ICU, etc).
- CRF 2 will capture operative information. Variables will include the type of surgery, date, time, and duration of surgery, blood loss and fluid replacement.
- CRF 3 will capture intervention-related data, including time of intervention, patient's systolic blood pressure and tourniquet pressure used, patient's pain scale as a result of the intervention, and whether or not the intervention was completed.
- CRF 4 will capture complication related data. All post-op complications will be graded I – V according to the Clavien-Dindo grading scale.[2] The number of each type of complications will be recorded. This data will be used to calculate CCI using an online calculator available at www.assesssurgery.com.[1]
- CRF 5 will capture data related to the molecular studies as discussed previously.

IX.3 Data Analyses

Methods of proposed data analyses are described in the Statistical analyses plan section, Appendix C.

X. Risks and Benefits

X.1 Risks to Subjects

In an awake patient (post-op), tourniquet inflation may cause pain. The investigators expect that the risk of pain overall is small. In a recently concluded pilot study of RIC in liver transplant recipients, a majority of subjects completed all four postoperative RIC interventions. The investigators anticipate that the proportion of subjects that would complete the two postoperative interventions in the proposed study would be either similar to the liver transplant recipient study or higher (because of 2 instead of 4 postoperative interventions). Importantly, the subjects will have the option to discontinue the research intervention if they perceive the pain as excessive.

There is a theoretical risk of ischemic injury to the limb receiving the RIC stimulus. However, no study using RIC previously has reported any such cases.[16–18] The investigators did not encounter any ischemic injury from tourniquet inflation in the liver recipient study.

Venipuncture has risks of bleeding and ecchymoses at the venipuncture site. However this risk is expected to be very small and not different from a routine blood draw. The amount of blood drawn for study purposes will be small (less than 50 mL total anticipated) and spread over a period of 3 days, and therefore is not expected to pose any risks to the subjects.

X.2 Benefits to Subjects

The anticipated benefit to subjects is fewer complications after major abdominal surgery. Fewer complications could lead to shorter hospital length of stays and possibly improved quality of life. In addition, the study is expected to provide valuable information regarding how RIC might modulate stress response to major surgery. It may help elucidate the pathways by which RIC modulates inflammation after surgery. If RIC reduces postoperative complications, data from this study would provide support for larger and more definitive studies.

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Appendix A – Abdominal Surgeries Considered for Study Inclusion

- Pancreatic resection
- Splenectomy
- Any gastrectomy (partial or total)
- Hiatal hernia repair
- Any gastric fundoplication
- Esophagectomy with planned intra-abdominal component
- Any hepatic resection
- Common bile duct exploration
- Resection of retroperitoneal sarcoma
- Any nephrectomy (partial or total)
- Hyperthermic intraperitoneal chemotherapy (HIPEC)
- Any colonic resection
- Colostomy or ileostomy takedown
- Repair of enterocutaneous fistula
- Open abdominal aortic aneurysm (AAA) repair
- Adrenalectomy

Additional operations will be considered for inclusion if the study team and primary surgical team both agree that the procedure is a major abdominal surgery, that the expected duration of the surgery will be $\geq$ 120 minutes, and the expected post-operative hospital length of stay will be $\geq$ 2 days.

Appendix B – Medications that would preclude subject enrollment

Sulfonylurea anti-diabetic agents

- Acetohexamide
- Carbutamide
- Chlorpropamide
- Glibenclamide (also known as glyburide)
- Glibornuride
- Gliclazide
- Glyclopyramide
- Glimepiride
- Glipizide
- Gliquidone
- Glisoxepide
- Tolazamide
- Tolbutamide

Nitrates

- Nitroglycerine (glyceryl trinitrate)
- Isosorbidemononitrate and dinitrate
- Itramin
- Pentaerithrityltetranitrate
- Propatylnitrate
- Tenitramine
- Trolnitrate
- Nicorandil