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

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Appendix C: Statistical Analysis Plan

I. Introduction

This plan provides a detailed description of the study endpoints, methods of data analyses and other relevant issues pertaining to a prospective randomized controlled trial of remote ischemic conditioning in patients undergoing major abdominal surgery at a single institution.

II. Study endpoints

II.1 Primary endpoint: 30 days postoperative complications

II.1.a The total complications burden up to 30 days after surgery will be evaluated with the use of comprehensive complications index (CCI, [range 0-100]).

II.2 Secondary enpoints

a) Length of hospital stay: number of days from surgery to discharge from hospital

b) 30-day mortality: (% subjects dying within 30 days)

c) Cytokine response: plasma levels (pg/mL) of TNF-a, IL - 1β, 6, 8 and 10

d) Acute phase response: Plasma levels of C-reactive protein (CRP), α-1 acid glycoprotein, fibrinogen and haptoglobin (mg/dL)

e) Complement activation: Plasma levels of C2, C4b, C5a and C5b-9 (mg/dL)

f) Leukocyte gene expression: Global gene expression changes in peripheral blood leukocytes

II.3 Feasibility/Acceptability endpoints

Feasibility: proportions of subjects completing all 3 assigned research interventions, not withdrawing participation and completing follow up after enrollment.

Acceptability: proportions of subjects not declining any of the 3 planned research interventions

II.4 Safety endpoints

a) Adverse events (AE)

b) Serious adverse events (SAE)

c) Adverse reactions (AR)

d) Suspected serious adverse reactions (SSAR)

e) Suspected unexpected serious adverse reactions (SUSAR)

The definitions of the safety endpoints are as per ICH Harmonized Tripartite Guideline for clinical safety data management E2A version 4.

III. Analyses populations

III.1 The primary analyses for efficacy will be conducted in an "**intent to treat (ITT) population** " that would include all randomized subjects.

III.2 Additional secondary analyses for efficacy will be conducted in "**per protocol (PP) population**" that would include only subjects that completed all three interventions and follow up.

III.3 The **Safety population** for analyses of safety endpoints will include all subjects that received at least one of the assigned interventions.

IV. Descriptive analyses

Demographic and clinical baseline characteristics will be summarized for each of the study groups. Data for continuous variables will be reported with point estimates (mean or median) and dispersion measures (standard deviation, 25th and 75th percentiles, 95% confidence intervals). Data for discrete variables will be reported as counts and proportions in each group. Counts of subjects with data missing for each variable will be reported.

No formal comparisons of the differences between the two groups are planned at present.

V. Analyses of study endpoints

V.1 Primary endpoint

Comprehensive complications index score will be compared between the two groups to examine the effect of RIC on postoperative complication. Data transformation may be utilized to achieve normality. One of two independent sample tests, a t test or Mann-Whitney test depending on the normality of distribution, will be used. Using multivariable regression exploratory analyses will be conducted to examine potential interactions of individual variables of age, sex and duration of surgery with RIC on CCI. P values of 0.05 will be considered significant.

V.2 Secondary endpoints

For endpoints that are continuous variables and are not normally distributed log transformation will be explored to achieve normality. Length of hospital stay will be compared with either a t test or Mann-Whitney test. Counts and proportions experiencing 30- day mortality will be reported. No formal intergroup comparison will be conducted regarding hospital stay and 30-day mortality.

The analyses to address the effects of RIC on plasma cytokines, acute phase response, complement activation and leukocyte gene expression will be considered independent of each other. Although these groups of outcomes are interconnected as a global innate immune responses to surgery or other injury it is quite likely that RIC may only modulate one or more rather than all the measured outcome subgroups. Furthermore, it is quite likely that RIC may modulate only one or few of the analytes in a particular subgroup

Repeated measures of continuous variables of inflammation, acute phase response and complement activation in two independent groups will be analyzed with mixed analyses of variance (ANOVA) to examined for interaction between treatment and time. If the omnibus p value is significant then additional post hoc tests will be conducted in appropriate groups. Because of the pilot nature of the study no adjustments will be made to the p values in the post hoc tests. P values <0.05 will be considered significant.

Leukocyte gene expression will be examined using RNA sequencing. Five to ten replicates in each group will be examined at baseline and postoperative day 2. A sequencing depth of 10 million reads will be utilized. Differential gene expression analyses will be performed. For individual genes with a relatively higher levels of expression relative fold changes of ≥ 2.0, and or p values of < 0.01 will be considered significant.

V.3 Feasibility/acceptability endpoints

The number of subjects meeting defined endpoints in each of the two study groups will be reported. No formal comparisons are proposed.

V.4 Safety endpoints

The number of subjects experiencing each of the safety endpoints will be reported separately for the two groups. No formal comparisons are proposed.

VI. Other considerations

VI.1 Missing data

Endpoints: The number of subjects in whom data would be missing is expected to be low due to the prospective nature of the study. The pattern of missing data will be described. Subjects with data missing for a particular outcome would be excluded from that analysis. Additional decisions about handling missing data would be made prior to any intergroup comparisons are performed.

Baseline values of continuous endpoints: Subjects in whom a baseline value of a continuous variable such as the laboratory analytes is missing will be included in the analyses of that outcome. A missing indicator approach, a valid method for prerandomization measures will be used.

VI.2 Multiple comparisons

Multiple comparisons will be performed only in the laboratory endpoints of inflammation, acute phase response and complement activation. P values for individual analytes will be reported. Due to the pilot nature of the study no adjustments to p values to accommodate multiple comparisons will be made.

VI.3 Subgroup analyses

No subgroups are defined a priori in the study protocol. Hence no subgroup analyses are proposed.

VI.4 Exploratory analyses

Exploratory analyses will be performed to examine whether age, sex and duration of surgery individually interact with RIC effects on the primary outcome and laboratory outcome parameters. For the primary outcome multivariable regression with interaction terms between a specified variable and RIC will be used. For the laboratory analytes a similar approach with mixed ANOVA will be used.

VI.4 Sample size and power

There is no data available in the literature regarding the potential benefits of RIC on global assessment of postoperative complications. Clinical trials of remote ischemic preconditioning, thus far were aimed at decreasing organ-specific complications such as myocardial infarction, acute kidney injury, stroke, etc. Data from animal studies of remote ischemic preconditioning or per- and postconditioning does not provide appropriate information. Therefore, evidence-based and realistic projections of effect size of the proposed intervention are not feasible. Hence, sample calculations and estimates of power were not pursued. It is anticipated that data on complications from this pilot study would assist in more informed calculations of sample size and power for future studies of similar nature.