Prevention of Post-Cardiac Surgery Acute Kidney Injury by Proton Pump Inhibitor: A Prospective Randomized Controlled Trial

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Statistical Analysis Plan

1. SYNOPSIS

The current study is single-center, randomized, controlled, single-blinded trial to determine whether perioperative intravenous administration of pantoprazole, a proton pump inhibitor (PPI), will reduce urinary kidney injury (AKI) biomarkers KIM-1 and other injury biomarkers, the incidence of AKI, and major adverse kidney events (MAKE) at POD 30 compared to famotidine after cardiac surgery with CPB. The specific aims of the study will be achieved by randomizing a cohort of 100 patients to receive pantoprazole (study) or famotidine (control) for 2 days perioperatively.

This Bayesian clinical trial will estimate the efficacy of PPI for the prevention of AKI with the primary outcome KIM-1, an indicator of AKI. Developing effective interventions for preventing AKI in the population experiencing renal ischemia requires incremental improvement of theoretically sound treatments based on systematically accruing data. Often such incremental development is hampered by statistical tools not appropriate to the task. Classical, Frequentist statistics have advanced the field, but are less informative for the initial evaluation of a new treatment. The reliance of the Frequentist framework on dichotomous, null hypothesis-testing provides some control of the error rate in the context of multiple repeated trials; however, this is not what early-phase treatment testing requires. Developing nascent treatments requires investigators to bet on an alternative hypothesis. Investigators evaluating a theoretically sound intervention want to know the probability that the approach confers some level of benefit given the observed data: that is, they want to know the probability that the alternative hypothesis is true. While Frequentist inference does not directly address this issue, Bayesian statistical inference provides a principled approach to answer this question. Indeed, addressing the so-called “Pipeline Problem” in developing clinical applications, the FDA has indicated that Bayesian statistics offers one avenue for improved methodological efficiency.[1–5]

Decision-making, based on an initial treatment trial, is assisted by estimates of the probability of an effect of some specified magnitude. These statements, not part of the conventional, Frequentist statistical lexicon, are accessible via Bayesian approaches, particularly with small sample sizes. [6,7] Detailed descriptions of Bayesian statistical reasoning exist elsewhere.[8,9] Succinctly, Frequentist models estimate the probability of observing the data (or data more extreme) given that the null hypothesis is true; Bayesian analyses estimate the probability of the alternative hypothesis given the observed data.[10] Bayesian probability estimates incorporate prior information about plausible parameter values (i.e., the prior distribution) and the observed data (i.e., the likelihood). Combining these two distributions forms the posterior distribution which permits evaluation of the probability that the true value of the parameter falls in some range.

2. GENERAL DATA ANALYTIC PLAN

2.1. Analysis Sample

The primary analysis sample for efficacy will implement intention-to-treat (ITT) principles. The safety evaluation will include all subjects while they were taking study treatment.

2.2. Patient Accountability and Compliance

A flowchart (CONSORT Diagram) will summarize participant status, listing the number and disposition of patients randomized to each treatment. Specifically, within each group, the

CONSORT Diagram will list the numbers of patients who completed the study, withdrew consent, death, and those lost to follow up.

2.3. Randomization

Randomization (1:1 ratio) with random blocks of 2 or 4.

2.4. Treatment Group Comparability

Initial analyses examining group differences for baseline variables will use cross-tabulation, ANOVAs, and examination of correlations between baseline variables and specified outcomes. For the purposes of evaluating the comparability of groups, a posterior probability of > 95% will constitute evidence for statistically reliable differences. Baseline or demographic variables on which group differences are detected, and which are correlated with outcomes, meet the definition of confounders[11,12] and will result in two sets of analyses: one in which the relevant variable is included as a covariate and one in which it is not. This will permit determination of the degree to which any group differences might confound conclusions regarding treatment.

2.5. Preliminary Analysis

For all continuous variables, outliers will be explored and extreme outliers will be queried to confirm that they are not erroneous before the data is locked for analysis, but outliers will not be removed from the analysis.

2.6. Multiplicity

In keeping with sound Bayesian analytic principles, salient error rates/operating characteristics for confirmatory analyses in each component of the trial, provided in the sample size justification section, result from Monte Carlo simulation. Any secondary analyses for which issues of multiplicity might be a consideration will use weakly, informative priors to regularize all estimates. Means for these regularizing priors will be centered on the null hypothesis, with variances determined by the scale of the data and credible effects previously reported in the literature in the most closely analogous studies. Of note is the principle that the more informative the priors are, based on credible estimates of these effects, the greater the degree of regularization, the more conservative the estimates, and the more likely the results are to replicate outside of the current sample. Indeed for any observed results, the Bayesian approach makes it possible to determine the sensitivity of the results to prior assumptions; the degree of prior skepticism an observer would require before dismissing the estimated treatment effect.[13] In the interest of transparency and reproducibility, the resulting reports will provide the prior specifications used for these secondary analyses.

2.7. Missing Data

Under the ITT principle, all patients who are randomized are included in the analysis. Therefore, missing data, especially in the primary outcome measure, can be problematic. Missing data will result in joint modeling of observed outcomes and the missing data which is robust to ignorable missingness.[14] Sensitivity analyses will evaluate robustness of analytic conclusions to missing data. Non-ignorable missing data patterns will be addressed through pattern-mixture modeling methods.[15]

2.8. Analysis Approach

Broadly, the data analytic strategy will use generalized linear and multilevel models (R and Stan) for both discrete, and continuous outcomes.[16–20] Multilevel generalized linear modeling to account for clustering of patients within site and repeated observations within patients will evaluate continuous, dichotomous, and count data.

Evaluation of posterior distributions will permit statements regarding the probability that effects of varying magnitudes exist, given the data. Specification of diffuse, neutral priors will reflect the initial uncertainty regarding effect sizes. For all generalized linear models, priors for (non-intercept) regression coefficients will be specified as ~Normal (μ=0, σ=1 x 1000), level one and two error variances will be specified as ~Exponential (μ=0, σ^2=1 x 10^3). The choice of prior distribution for level two variances will follow Gelman's recommendations.[9] Priors for the comparison of proportions will be specified as ~Beta (α=1.0, β=1.0).

2.9. Specific Data Analytic Models

Generalized linear modeling will evaluate continuous outcomes as follows.

Residualized change model at hour 8, 24, or 48:

$$y = \beta_0 + \beta_1 Baseline_1 + \beta_2 Treatment_1$$

Generalized linear multilevel model:

$$y = \beta_0 + \beta_1 Treatment_1 + \beta_2 Time_1 + \beta_3 (Treatment_1 \times Time_1)$$

Where *y* (i.e., KIM-1 levels) may follow a variety of response distributions including: 1) Normal, 2) T-distribution, 3) Gamma, 4) Log-Normal, 5) Hurdle-Gamma, 6) Hurdle-Log-Normal, 7) Cumulative Logit, and 8) Adjacent-Category models.

Hypothesis 1.1: We hypothesize that perioperative administration of the PPI pantoprazole would reduce KIM-1, a urinary biomarker of AKI, in cardiac surgery patients compared to famotidine. Measurement of KIM-1 will occur at baseline and post-operatively at hours 8, 24 and 48. The primary outcome point will be area under the curve (AUC) of KIM-1 above baseline within 24 hours postoperatively. Additionally, models will estimate KIM-1 at 48 hours. Generalized linear modelling will evaluate KIM-1 at 48 hours as a function of treatment condition, adjusting for baseline KIM-1. Secondarily, similar models will evaluate KIM-1 at 8 and 24 hours after adjusting for baseline KIM-1. Additional secondary analyses will use generalized linear multilevel models to evaluate KIM-1 as a function of time, treatment condition and the interaction of time and treatment.

Hypothesis 2.1: We hypothesize that administration of the PPI pantoprazole will reduce other urinary kidney injury biomarkers (NGAL, TIMP-2, and IGFBP-7). The primary outcome point will be area under the curve (AUC) of each of these biomarkers above baseline within 24 hours postoperatively. Additionally, models will estimate each biomarker at 48 hours. Generalized linear modelling will evaluate biomarkers at 48 hours as a function of treatment condition, adjusting for baseline levels. Secondarily, similar models will evaluate biomarkers at 8 and 24 hours after adjusting for baseline levels. Additional secondary analyses will use generalized linear multilevel models to evaluate each biomarker as a function of time, treatment condition and the interaction of time and treatment.

Hypothesis 2.2: We hypothesize that administration of the PPI pantoprazole will reduce the incidence, severity and duration of acute kidney injury (AKI) in cardiac surgery patients compared to famotidine as measured at hospitalization day 30. Generalized linear modelling will evaluate the incidence, severity and duration of AKI at day 30.

Hypothesis 2.3: We hypothesize that administration of the PPI pantoprazole will reduce the incidence of MAKE in cardiac surgery patients compared to famotidine as measured at hospitalization day 30. Generalized linear modelling will evaluate the incidence of MAKE at day 30.

2.10. Safety Analyses

All adverse events and serious adverse events will be modelled as a function of treatment group, using the beta-binomial distribution.

2.11. Exploratory Outcomes

Additional clinical outcomes (maximal change in creatinine by POD 7; postoperative ventilation time, re-intubation, postoperative myocardial infarction, postoperative delirium, infection and ICU and hospital length of stay) will be modeled as a function of treatment group.

2.12. Safety Monitoring

Safety monitoring will occur via the DSMB in accordance with FDA AE and SAE reporting requirements with interim safety evaluations every three months.

2.13. Sensitivity Analysis

Per protocol analyses will evaluate only those participants treated according to the protocol using the same methods described above and applied to the ITT analysis. Inconsistencies with the primary ITT analysis will result in cautious interpretation of the trial findings.

2.14. Subgroup Analyses by Gender, Race, Ethnicity

Secondary analyses will evaluate heterogeneity of treatment effect as a function of gender, age, ethnicity and NIAID-OS strata. The approach to subgroup analyses will utilize skeptical, informative priors to increase the likelihood of future replication.[21,22]

3. DETERMINATION OF SAMPLE SIZE

This is a pilot feasibility study. We will use the preliminary data achieved with this study proposal for further larger-scale trials and external funding applications. Therefore, no sample size calculation will be needed.

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