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

NCT06154226

Date: 11/10/23

Protocol

DEPARTMENT OF ANESTHESIOLOGY CLINICAL PROTOCOL SUMMARY

Protocol Title:

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

Principal Investigator:

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- Charles Green, Ph.D. – Collaborator

Study Coordinator: Connor Rollings

Population:	100 adult patients presenting for cardiac surgery with cardiopulmonary bypass at the Memorial Hermann Hospital TMC.
Number of Sites:	Single site / Memorial Hermann TMC
Study Duration:	1-2 years
Subject Duration:	30 days

A. INTRODUCTION / BACKGROUND

Each year more than 500,000 cardiac surgeries are performed in the USA alone. AKI is a common complication following cardiac surgery and is associated with poor patient outcome and increased health care cost.[1,2] Therefore, there is an urgent need to identify medical interventions and treatments that prevent AKI or mitigate its severity when it occurs after cardiac surgery.

One of the main causes of AKI following cardiac surgery involves renal hypoperfusion/ischemia and reperfusion injury.[3,4] Hypoxia inducible factors (HIFs) are key transcription factors responsible for tissue adaptation to low oxygen, which orchestrate the expression of a wide variety of genes including a set of microRNAs.[5,6] MicroRNAs are endogenous single-stranded noncoding miRNAs of nucleotides that participate in physiological and pathological functions via regulating post-transcription of target genes. During ischemic injury, hypoxia upregulates endothelial MicroRNAs that has a potential in renal protection through vascular integrity and regeneration. Additionally, microRNAs exerts protective effects via decreasing apoptosis and promoting tubular cell proliferation during ischemic AKI.

Moreover, decreased serum levels of MicroRNAs are highly correlated with AKI severity in the intensive care unit (ICU) patients.

Our preliminary study identified ATP4A as the downstream target gene of MicroRNAs in the kidney. ATP4A (catalytic α subunit of H+/K+ ATPase) is located in intercalated cells in the distal tubules and cortical collecting ducts, which regulates urine acidification through secretion of hydrogen and reabsorption of potassium from urine. Proton pump inhibitors (PPIs) block the ATP hydrolysis of the H+/K+ ATPase via binding its active site of ATP4A and further enhance this endogenous kidney protection pathway. Despite robust animal model data, randomized controlled trial aiming to test the effectiveness of PPI in post-cardiac surgery AKI prevention is lacking. If proven to be effective, our studies could be easily implemented in clinical practice and serve as an effective treatment for perioperative AKI.

B. HYPOTHESIS

We hypothesize that perioperative administration of PPI pantoprazole could reduce acute kidney injury following cardiac surgery.

B. SPECIFIC AIMS

Aim 1: To determine whether perioperative intravenous administration of pantoprazole (study group) will reduce urinary kidney injury biomarkers KIM-1 following cardiac surgery with cardiopulmonary bypass compared to famotidine (control group) (n=100 total; primary endpoint).

Aim 2: To determine whether perioperative intravenous administration of pantoprazole will increase other urinary kidney injury biomarkers (NGAL, TIMP-2, and IGFBP-7), the incidence of postoperative AKI and major adverse kidney events (MAKE) at POD 30.

C. RESEARCH STRATEGY

1) Significance/Rationale

   a. AKI is a common complication following cardiac surgery and is associated with increased postoperative morbidity, prolonged hospitalization, progression to chronic kidney disease, and increased short and long-term mortality. Although clinical definitions, biomarkers, and pathophysiology of AKI are intensively studied, clinical approaches to treat or prevent AKI are lacking. Based on animal studies, the opportunity to prevent AKI is an easier goal than the reversal of established AKI. In the perioperative setting most elective surgeries are carried out in patients without AKI. Therefore, prophylactic approaches to prevent AKI in patients undergoing surgeries would have a major impact. If the current proposal is successfully completed, PPIs such as pantoprazole could be given prophylactically throughout the perioperative period to prevent AKI. This could represent the first clinical approach for perioperative AKI prevention or treatment.

2) Protocol

- Experimental Design/Flowchart

Overview: The central hypothesis of this proposal is that perioperative administration of PPI pantoprazole could reduce acute kidney injury following cardiac surgery by enhancing the endogenous pathway for kidney protection. We propose a single-center, randomized, controlled, single-blinded trial to determine whether perioperative intravenous administration of pantoprazole will reduce urinary kidney injury 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.

Intervention: Patients will be randomized to receive pantoprazole (40 mg iv q12H) vs. famotidine (20 mg iv q12H) for 2 days perioperatively (first dose after anesthesia induction and before surgical incision, second dose at chest closure, then followed by 2 doses daily (Q12hr dosing) on POD 1 for a total of 4 doses over 2 days. There will be no other modifications in patient care. Both pantoprazole and famotidine are the standard medications used for GI prophylaxis at the current institution.

Prospective in-Hospital Data Collection: Each patient will be followed daily until POD 30 or discharge (whichever is earlier). Primary hospitalization data including subjects' demographics, co-morbidities, medications and other relevant preoperative clinical data as well as intraoperative information and postoperative outcomes and complications (specifically nosocomial pneumonia and C-Diff colitis) will be collected by trained research personnel using a detailed case report form. Data will be stored electronically and maintained in a secured computerized database.

Blood and Urine Samples Collection: Laboratory tests will be collected according to institutional protocols and standard of care. For each patient urine samples will be collected at 5 time points: baseline after induction of anesthesia and prior to administration of first dose of study medication, at chest closure before the second dose of the study medication, 8 hours after ICU admission, and then 24, and 48 hours after ICU admission. Urine samples will be used to measure urine acidity and kidney injury biomarkers (KIM-1, NGAL, TIMP2 and IGFBP-7) for the 5 study points. Blood samples will be used to measure kidney function parameters (for the complete hospitalization period according to institutional practice). All the tests performed, and the time points are standard of care at current institution except for the urinary kidney injury biomarkers. The urinary samples for biomarker study will be stored in regular urine analysis container and then transported to the medical school 5.026, Dr. Eltzschig's

laboratory. The sample will be stored for up to 2 days until they are analyzed. The container will be labeled with study ID, no patient identifier will be shown on the container.

- Inclusion/Exclusion Criteria

  Inclusion - Adult patients (age 18-90) that are scheduled for elective cardiac surgery with CPB with moderate to high risk of developing AKI (Cleveland risk score equal or higher than 3, please see the appended table at end of the revised protocol) will be enrolled for the study.
  Exclusion - Patients who have preoperative eGFR<30 ml/min per 1.73 m2 or dialysis dependence will be excluded from the study. In addition, emergency surgery, pregnancy or nursing patient, patients with interstitial nephritis, PPIs hypersensitivity, liver disease, or vitamin B12 deficiency will be also excluded.

- Primary and Secondary End Points

  The primary outcome will be the area under the curve (AUC) of urinary kidney injury biomarker KIM-1 above baseline within 24 hours postoperatively. Secondary outcome will be the area under the curve (AUC) of other urinary kidney injury biomarkers (NGAL, TIMP-2, and IGFBP-7) above baseline within 24 hours postoperatively, and the composite result of the incidence of any-stage postoperative AKI within 7 days of surgery (or until hospital discharge if earlier) and incidence of MAKE at 30 days. AKI will be defined using the 2012 Kidney Disease Improving Global Outcomes (KDIGO) criteria: SCr increase greater than 50% from baseline or $\geq$ 0.3 mg/dL increase within 48 hours after surgery. The urine output criteria will not be used to determine AKI. MAKE is defined as the composite of death, dialysis, renal hospitalization or sustained kidney dysfunction (GFR decline of 25% or more from preoperative baseline) at 30 days after surgery. Additional clinical outcomes that will be collected include AKI severity in each group; maximal change in creatinine by POD 7 in each group; postoperative ventilation time, re-intubation, postoperative myocardial infarction, postoperative delirium, infection and ICU and hospital length of stay.

- What is routine clinical care for the conditions being studied?

  Both pantoprazole and famotidine are the standard medications used for GI prophylaxis at the current institution. The patient will receive either medication for GI prophylaxis after cardiac surgery.

- Safety and Adverse Events:

  Due to the simple study design and essentially just following the standard of care at the current institution, we do not expect major issues with patient enrollment or study protocol execution. Any adverse events such as c.diffile colitis, nosocomial pneumonia will be reported.

The Data Monitoring and Safety Board (DMSB) will consist of members from departmental research committee, a cardiac anesthesiologist, a cardiac surgeon and an intensivist. They will review the safety of the study protocol **every 6 months** to ensure safe execution of the research protocol.

- Are study risks accurately described (if any)?
  Due to the simple study design and essentially just following the standard of care at the current institution, we do not expect major issues with patient enrollment or study protocol execution.

3) Statistical Plan

- Sample size and statistical analysis *(see attachment)*
  - 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.

Ethics: Written informed consent will be obtained. Patients will be approached at the preoperative holding area or on the ward and offered participation in the trial. The person who obtains research consent should not be directly related with patient's care. Benefits and risks of participating the study will be explained to the patient in detail, all questions shall be answered.

- Subject Selection and Withdrawal
  Patients will be approached at the preoperative holding area or on the ward and offered participation in the trial. Once informed consent is obtained, patients will be enrolled and randomized to pantoprazole or famotidine by trained research coordinators using a computerized randomization software and provided with pantoprazole or famotidine based on their randomization. Enrolled patients cannot participate in other studies investigating post-cardiac surgery AKI. Patients have the right to withdraw from the study at any point.

Data handling and record keeping

- Patient's data will be accessed through Care 4 electronic medical record system at MH TMC. All reasonable efforts will be made to keep each patient's protected health information (PHI) private and confidential. There will be limited access to medical records and de-identification of all records. Potential human subjects for the study will be identified through MHTMC operating room tracker.
- The patient data will be linked to study ID. The linkage is stored in a centered password protected UTHealth computer, only study key personnel has access to the linkage data. The data collection form and consent form will be stored in a secured office for 3 years.
- Data will be stored in secured areas on password protected UTHealth PCs conforming to the latest UTHealth IS security policies. Computer databases will be maintained on password

protected UTHealth PCs. All study staff have completed employee education regarding patient confidentiality and have completed Human Subjects protection education (CITI course) as specified by the UTHealth IRB. Research Records will be retained for a period of 3 years after the submission of the final report and close-out procedures on the research project for which the Research Records were prepared. The retention of the original Research Records shall be the responsibility of the Principal Investigator.

References:

1. O'Neal JB, Shaw AD, Billings FTt. Acute kidney injury following cardiac surgery: current understanding and future directions. *Crit Care.* 2016;20(1):187.
2. Wang Y, Bellomo R. Cardiac surgery-associated acute kidney injury: risk factors, pathophysiology and treatment. *Nat Rev Nephrol.* 2017;13(11):697-711.
3. Eltzschig HK, Carmeliet P. Hypoxia and inflammation. *N Engl J Med.* 2011;364(7):656-665.
4. Eltzschig HK, Eckle T. Ischemia and reperfusion--from mechanism to translation. *Nat Med.* 2011;17(11):1391-1401.
5. Eltzschig HK, Bratton DL, Colgan SP. Targeting hypoxia signalling for the treatment of ischaemic and inflammatory diseases. *Nat Rev Drug Discov.* 2014;13(11):852-869.
6. Eckle T, Hartmann K, Bonney S, et al. Adora2b-elicited Per2 stabilization promotes a HIF-dependent metabolic switch crucial for myocardial adaptation to ischemia. *Nat Med.* 2012;18(5):774-782.

Risk factor	Points
Female gender	1
Congestive heart failure	1
Left ventricular ejection fraction <35%	1
Preoperative use of IABP	2
COPD	1
Insulin-requiring diabetes	1
Previous cardiac surgery	1
Emergency surgery	2
Valve surgery only (reference to CABG)	1
CABG+valve (reference to CABG)	2
Other cardiac surgeries	2
Preoperative creatinine 1.2 to 2.1 mg/dl (reference <1.2)	2
Preoperative creatinine >2.1 (reference to <1.2)	5
Minimum score, 0; maximum score, 17	

IABP = Intra aortic baloon counterpulsation; COPD = Chronic obstructive pulmonary disease; CABG = Coronary artery bypass graft

Table 1: Cleveland Risk Score for acute kidney injury.