Impact of ketamine versus propofol for anesthetic induction on acute kidney injury and renal biomarkers in cardiac surgery

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Research Plan

We propose a prospective study in which the effects of ketamine on acute kidney injury in cardiac surgery are investigated in adult cardiac surgical procedures requiring cardiopulmonary bypass (CPB). Ketamine has been demonstrated to have an anti-inflammatory effect as shown by reductions in Interleukin 6 (IL-6) levels. Postoperative dysfunctions in which inflammation has been implicated may be reduced by this anti-inflammatory effect. Use of inotropic and vasopressor support, hemodynamic variables, incidence of renal dysfunction, and effect on biomarkers of renal function will be assessed in the early postoperative period. Specifically, we will test the hypothesis that ketamine provides anti-inflammatory effects in this population of patients undergoing surgery requiring CPB and that the incidence of renal dysfunction will be decreased.

Background and Significance

Ketamine is an FDA approved non-barbiturate anesthetic and acts as an N-methyl-D-aspartate (NDMA) receptor antagonist. This medication is commonly used in the induction of anesthesia as well is in the performance of sedation for procedures. Ketamine has been demonstrated in several studies to have anti-inflammatory effects.[1–4] In cardiac surgical patients, the inflammatory response stimulated by undergoing cardiopulmonary bypass is thought to contribute to postoperative organ system dysfunction and morbidity. A reduction an inflammatory mediators has been shown in patients receiving ketamine prior to undergoing cardiac surgical procedures, including reductions in IL-6, cardiac troponin I (cTnI), and creatine kinase MB (CK-MB). IL-10 has anti-inflammatory effects and has been shown to be increased in patients who received preoperative ketamine compared with patients who did not.[1,4] In a group of patients who did not receive ketamine, IL-6 values peaked at 6 hours following aortic cross clamp, but this rise in peak was not seen in a group of patients who received a continuous ketamine infusion.[4]

A review and meta-analysis examined 14 studies involving 684 patients undergoing a variety of surgical procedures including coronary artery bypass graft (CABG) surgery and found that ketamine does decrease IL-6 concentration. Elevations in IL-6 have been associated with ventricular wall motion abnormalities, perioperative complications, postoperative hemodynamic instability, postoperative cognitive dysfunction, renal dysfunction, severity of acute respiratory distress syndrome, and in children, morbidity and mortality after cardiac surgery.[1,5]

Acute kidney injury (AKI) remains a significant issue following cardiac surgery and is associated with both increased morbidity and mortality.[6] Although the incidence of AKI varies

depending on the type of surgery and definition of AKI used, it has been reported to occur in 20-38% of cases.[7–9] Patients developing AKI are at increased risk for chronic kidney disease (CKD) as well as end-stage renal disease (ESRD) with those who require renal replacement therapy being more than 3 times as likely to progress to ESRD.[10] Postoperative AKI is likely to be multifactorial with ischemia, reperfusion, and inflammation all playing a role.[10,11] Thus, any potentially modifiable factors need to be evaluated thoroughly.

Several renal biomarkers have been suggested for use in cardiac surgery to identify patients either at risk for acute kidney injury (AKI) or those who develop it postoperatively, such as Cystatin C, NGAL, and TIMP2-IGFBP7. Changes in these biomarkers occurs more quickly than changes in serum creatinine allowing for identification of patients earlier. Currently, our practice does not utilize renal biomarkers for identification of patients at increased risk for postoperative AKI, however, it has been recommended in guidelines.[10]

Preliminary Data

A pilot study was designed to elucidate potential clinical benefits of the anti-inflammatory effects of ketamine looking at the outcomes acute kidney injury, cognitive function, and delirium. As such, patients at high risk of postoperative AKI were included, specifically those undergoing multi-valvular and complex cardiac procedures with advanced age. A total of 49 patients were included (25 ketamine, 24 propofol). Acute kidney injury (AKI) was assessed using Kidney Disease Improving Global Outcomes criteria and occurred in **12 (50%)** patients in the propofol group and **6 (24%)** patients in the ketamine group (p=0.08; Relative Risk=2.1, 95% CI 0.9 to 4.7). No difference in postoperative cognitive dysfunction or delirium was seen alleviating concerns regarding ketamine and cognitive issues. This study was registered at

ClinicalTrials.gov (NCT02554253) and the manuscript has been submitted for publication. Reliable techniques to reduce AKI are not available beyond maintaining adequate hemodynamics and flow making this signal of high interest to the care of these patients. Due to the significant negative impact on patient's lives following suffering acute kidney injury, a larger study is warranted to confirm and further elucidate this important finding.

Specific Aims/Hypotheses:

We aim to determine the impact of ketamine versus propofol administration at induction of anesthesia on postoperative renal dysfunction, intra and postoperative hemodynamics and requirement for inotropic and vasopressor support, and postoperative renal biomarkers.

Specific Aim 1: 1. Determine the incidence of renal dysfunction in patients who receive ketamine for induction compared with those who receive propofol.

Specific Aim 2: Determine the impact of ketamine on patient hemodynamics as well as the dose of vasopressor and inotropes used during the intra and postoperative periods.

Specific Aim 3: Determine the association of three renal biomarkers with the development of acute kidney injury in the postoperative period and the feasibility of incorporating these into standard clinical practice.

Study Design

Institutional review board (IRB) approval will be obtained for the study design and written informed consent will be obtained from each patient. The study will be registered at ClinicalTrials.gov. We propose a prospective study in which patients will be randomized for induction with ketamine versus propofol (another standard anesthesia induction agent) and both are FDA approved for this indication. Hemodynamics before, during, and after cardiopulmonary bypass and use of inotropic and vasopressor medications will be recorded as per usual charting. The incidence of renal dysfunction, AKI as defined by Kidney Disease Improving Global Outcomes (KDIGO) criteria, will be compared between the ketamine and propofol groups as will the changes in biomarkers of renal function which can indicate kidney injury has occurred earlier than a rise in creatinine.

Inclusion/Exclusion Criteria

We will include patients age greater than or equal to 70 years presenting for cardiac surgery at the Mayo Clinic in Rochester, Minnesota. Patients will be eligible for inclusion if they are scheduled to undergo complex cardiac surgery. Complex cardiac surgery will be defined as surgery involving more than one heart valve, any redo-sternotomy procedures, or combined valvular and CABG procedures. Aortic repair procedures will not be excluded if meets other criteria. Exclusion criteria will include left or right ventricular assist device implantation or explantation, procedures not requiring cardiopulmonary bypass, active infection or sepsis requiring antimicrobial therapy and/or vasopressor therapy (treated endocarditis is not excluded), severe hepatic disease resulting in ascites, pre-operative significant renal dysfunction including a baseline creatinine equal to or greater than 2 mg/dL or requiring dialysis, immunosuppressive

medication use (including current IV or oral steroids use, use of anti-rejection medications for transplant within 1 month, or chemotherapy within 6 months), or immunodeficiency syndrome including HIV/AIDS, leukemia, and multiple myeloma.

Number of subjects

Although the incidence of AKI varies depending on the type of surgery and definition of AKI used, it has been reported to occur in 20-38% of cases.[7–9] In the preliminary data presented above the incidence in our population was as high as 50% which is reasonable considering the high risk population selected. Taking a more conservative approach and estimating the true incidence of renal dysfunction in the propofol group was 45% and in the ketamine group was 25%, the number needed to enroll for this study would be 180 patients for 80% power. We will aim to enroll 200 patients, with 100 in each group, to allow for protocol deviation or other source of study drop out.

Randomization and Consent

Written, informed consent will be obtained. The study will be minimal risk and non-invasive. Ketamine and propofol are both standard and commonly used medications for the induction of anesthesia. A small volume of blood (1/2 teaspoon) will be drawn to measure the urinary biomarker Cystatin C at 4 hours postoperatively via standard invasive lines placed for the surgical procedure. Urine samples (2 teaspoons) will be taken via foley catheter at 4 hours postoperatively for measurement of the urinary biomarkers NGAL, TIMP-2, and IGFBP7. All aspects of care will be as per usual for patients undergoing these operations at The Mayo Clinic. Subjects will be recruited by review of the surgical schedule. Randomization will occur

following informed consent and prior to surgery. A member of the study team will communicate to the OR staff prior to surgery the induction medication to be used.

Human Subjects

Detailed Description: The human subjects will be prospectively studied after being randomized to receive one of two commonly used anesthesia induction agents.

Population: The subject population in this study will include all patients admitted to Mayo Clinic Rochester for cardiac surgery that meet the inclusion criteria. No specific populations (regardless of race, ethnicity, or gender) will be excluded from this study aside from those who meet the exclusion criteria described above.

Research Materials: Electronic data will be stored securely and only accessed by those authorized on the IRB application.

The study will be minimal risk and written, informed consent will be obtained.

Potential Risks: This study compares two commonly used anesthetic agents. This study will not increase the risk of physical harm beyond what the surgical procedure naturally carries. The only potential risk is a breach of confidentiality, but this is thoroughly addressed as described below.

Protection: Data will be collected and stored on a secure Mayo server in a password-locked folder. No patient names will be stored, and the only identifiers included in the data will be clinic number, date of birth and date of admission. Only study team members listed on the IRB will be allowed access to the study data.

Protocol/Methods

Written, informed consent will be obtained. Anesthetic management will be directed by the consultant anesthesiologist as per routine aside from the following: Patients will be randomized to ketamine (1-2 mg/kg) versus propofol (0.5-1 mg/kg) induction with additional medication administered as needed to achieve intubating conditions. Inhalation anesthetic for induction in combination with either propofol or ketamine will be permitted. The ketamine group will not receive propofol and vice versa. Analgesic regimen will be per current multimodal guidelines. Albumin administration will be avoided, but ultimately left to the discretion of the consultant anesthesiologist. Invasive monitoring techniques will be left to the discretion of the consultant anesthesiologist as per routine.

All other aspects of patient care will be as per routine including administration of inotropic or vasopressors as needed at the discretion of the anesthesiologist and /or cardiac surgical team. Administration of inotropic or vasopressors will be recorded in the anesthesia record as per usual practice.

A small volume of blood (1/2 teaspoon) will be drawn via existing arterial or venous lines for Cystatin C at 4 hours post operatively in the ICU. Urine samples (2 teaspoons) will be taken via the foley catheter 4 hours post operatively.

Outcome measurements

After inclusion in the study, demographic and medical data from all patients including age, height, weight, medical co-morbidities and current medications will be recorded and saved in the database. In addition, information regarding the planned procedure and the specifics of each patient's cardiac disease including ventricular function, current cardiac anatomy and details of

previous cardiac repairs will be recorded. Liver and renal function will be assessed by recording liver function tests and renal indices if available in the preoperative medical record.

Our primary outcomes will be the incidence of renal dysfunction. Secondary outcomes will include assessing differences in hemodynamics, inotropic use, and vasopressor use between the ketamine and propofol group as well as differences in biomarkers of renal function. The feasibility of utilizing biomarkers in the clinical care of patients will be assessed based on availability of data and correlation with renal dysfunction. Mortality during admission for cardiac surgery will be assessed, however, the study will not be powered for this to be a primary outcome measure.

Patients undergoing cardiac surgery with cardiopulmonary bypass are at risk for numerous adverse events simply as a result of their admitting diagnosis. This study is minimal risk and we will not observe for any adverse events aside from hemodynamic collapse at the time of induction.

Data Analysis

Incidence of renal dysfunction will be expressed as a percentage. Values will be compared between ketamine and non-ketamine groups using *t*-tests and ANOVA. A P value of less than 0.05 will be considered significant. Secondary outcomes will be analyzed using a t-test or ANOVA. All comparisons will be completed adjusting for multiple comparisons using the Bonferroni method.

References

1. Dale O, Somogyi AA, Li Y, Sullivan T, Shavit Y. Does intraoperative ketamine attenuate inflammatory reactivity following surgery? A systematic review and meta-analysis. *Anesth Analg*. 2012;115(4):934-943. doi:10.1213/ANE.0b013e3182662e30

2. Hudetz JA, Patterson KM, Iqbal Z, et al. Ketamine attenuates delirium after cardiac surgery with cardiopulmonary bypass. *J Cardiothorac Vasc Anesth*. 2009;23(5):651-657. doi:10.1053/j.jvca.2008.12.021

3. Riha H, Kotulak T, Brezina A, et al. Comparison of the effects of ketamine-dexmedetomidine and sevoflurane-sufentanil anesthesia on cardiac biomarkers after cardiac surgery: an observational study. *Physiol Res*. 2012;61(1):63-72. http://www.ncbi.nlm.nih.gov/pubmed/22188112

4. Welters ID, Feurer MK, Preiss V, et al. Continuous S-(+)-ketamine administration during elective coronary artery bypass graft surgery attenuates pro-inflammatory cytokine response during and after cardiopulmonary bypass. *Br J Anaesth*. 2011;106(2):172-179. doi:10.1093/bja/aeq341

5. Musleh GS, Datta SS, Yonan NN, et al. Association of IL6 and IL10 with renal dysfunction and the use of haemofiltration during cardiopulmonary bypass. *Eur J Cardiothorac Surg*. 2009;35(3):511-514. doi:10.1016/j.ejcts.2008.10.010

6. Fuhrman DY, Kellum JA. Epidemiology and pathophysiology of cardiac surgery-associated acute kidney injury. *Curr Opin Anaesthesiol*. Published online 2017. doi:10.1097/ACO.0000000000000412

7. Garg AX, Devereaux PJ, Yusuf S, et al. Kidney function after off-pump or on-pump coronary artery bypass graft surgery: a randomized clinical trial. *JAMA*. 2014;311(21):2191-2198. doi:10.1001/jama.2014.4952

8. Schopka S, Diez C, Camboni D, Floerchinger B, Schmid C, Hilker M. Impact of cardiopulmonary bypass on acute kidney injury following coronary artery bypass grafting: a matched pair analysis. *J Cardiothorac Surg*. 2014;9(1):20. doi:10.1186/1749-8090-9-20

9. Yoo YC, Shim JK, Song Y, Yang SY, Kwak YL. Anesthetics influence the incidence of acute kidney injury following valvular heart surgery. *Kidney Int*. 2014;86(2):414-422. doi:10.1038/ki.2013.532

10. Nadim MK, Forni LG, Bihorac A, et al. Cardiac and Vascular Surgery-Associated Acute Kidney Injury: The 20th International Consensus Conference of the ADQI (Acute Disease Quality Initiative) Group. *J Am Hear Assoc*. 2018;7(11). doi:10.1161/JAHA.118.008834

11. O'Neal JB, Shaw AD, Billings FT. Acute kidney injury following cardiac surgery: Current understanding and future directions. *Crit Care*. Published online 2016. doi:10.1186/s13054-016-1352-z