THE IMPACT OF KETAMINE ON POSTOPERATIVE COGNITIVE DYSFUNCTION, DELIRIUM, AND RENAL DYSFUNCTION IN PATIENTS 70 YEARS OF AGE OR OLDER AND UNDERGOING CARDIAC SURGERY.

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RESEARCH PLAN

We propose a prospective study in which the effects of ketamine in cardiac surgery are investigated in adult patients undergoing 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 and cognitive dysfunction, and incidence of delirium will be assessed. 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 and cognitive dysfunction and delirium will be decreased.

Background and Significance

Ketamine is an FDA approved nonbarbiturate anesthetic and acts as a N-methyl-D-aspartate (NMDA) receptor antagonist. This medication is commonly used in the induction of anesthesia as well as 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 CPB is thought to contribute to postoperative organ system dysfunction and morbidity. A reduction in 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 receive ketamine.[1, 4] In a group of patients who did not receive ketamine, IL-6 values peaked at 6 hours following aortic cross clamp removal, but this rise and peak was not seen in the 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. This concluded that ketamine does decrease IL-6 concentration. Elevations in IL-6 have been associated with ventricular wall motion abnormalities, perioperative complications, postoperative hyperdynamic instability, postoperative cognitive dysfunction, renal dysfunction, severity of acute respiratory distress syndrome (ARDS), and morbidity and mortality in children after cardiac surgery.[1, 5]

Results are conflicting regarding the impact of ketamine on CRP. In two reports postoperative CRP levels were lower in the group of patients who received pre-operative ketamine compared to those who received placebo.[2, 6] However, in a study comparing patients receiving a continuous ketamine infusion versus those not receiving ketamine, IL-6 and IL-8 levels were reduced in the ketamine group, but CRP levels were not different at 24 hours postoperatively.[4]

Postoperative cognitive dysfunction and postoperative delirium are important areas of morbidity following cardiac surgery. Unrelated to cardiac surgery, a systematic review confirmed an association between elevated inflammatory markers and poor cognitive outcomes.[7] In cardiac surgical patients, elevated IL-6 and CRP levels have been shown to be associated with worse cognitive function following CABG surgery.[6] Ketamine is thought to be neuroprotective, with multiple possible mechanisms having

been proposed, although the exact mechanism has not yet been elucidated.[2] Interestingly, ketamine has been shown to be associated with a decreased incidence of delirium and these patients also had lower postoperative CRP levels. In this study the incidence of delirium was reduced from 31% in the control group to 3% in the ketamine group.[2] In patients undergoing cardiac surgery polymorphisms in the 5HT2a receptor gene and NMDA receptor 3A and 2B subunits genes were investigated for association with postoperative delirium. A genetic variation, the presence of the AG haplotype of the GRIN3A gene, of the NMDA receptor was independently associated with postoperative delirium.[8] Additionally, when examining patients who developed delirium those with the AG haplotype suffered from delirium longer than patients with the GG haplotype. This may be a potential avenue by which ketamine impacts delirium. Postoperative delirium is associated with increased morbidity and mortality as well as increased hospital length of stay.[9, 10] If ketamine administration does prove to reduce delirium, it could make a significant impact on morbidity and mortality following cardiac surgery as delirium has proven difficult to prevent and treat.

Renal dysfunction is another significant area of morbidity in patients following cardiac surgery and has been associated with increased mortality.[11] Although no data has demonstrated an association between ketamine and a decrease in renal dysfunction, elevated postoperative IL-6 levels, measured 12 hours following surgery, have been associated with an increased incidence of renal dysfunction following surgery utilizing CPB.[5] One study demonstrated a decreased incidence of acute kidney injury (AKI) in patients who received propofol compared to those who received sevoflurane and another study demonstrated a decreased incidence of AKI in patients receiving a post-CPB

dexmedetomidine infusion.[12, 13] It is reasonable to postulate that the anti-inflammatory properties of ketamine as revealed by decreased levels of the inflammatory marker IL-6 may be associated with a decrease in postoperative renal dysfunction.

Patient age (> 65 years) and increased surgical complexity (with longer operative times) are known risk factors for postoperative cognitive dysfunction, delirium, and renal dysfunction.[14-16] These higher risk patients would be the population that would benefit most from the potential decrease in these important areas of morbidity.

Specific Aims/Hypotheses:

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

Specific Aim 1: 1. Determine the incidence of cognitive dysfunction and delirium 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 incidence of renal dysfunction, defined by AKIN criteria, in patients who receive ketamine for induction compared with those who receive propofol.

STUDY DESIGN

We propose a prospective study in which patients will be randomized for induction with ketamine versus propofol (another regularly used anesthesia induction agent). Hemodynamics before, during and after cardiopulmonary bypass and use of inotropic and vasopressor medications will be recorded as per usual charting. The incidence of delirium, cognitive dysfunction, and renal dysfunction will be compared between the ketamine and propofol groups.

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 schedule to undergo complex cardiac surgery. Complex cardiac surgery will be defined as surgery involving more than one heart valve, redo-sternotomy procedures, or combined valvular and CABG procedures. Exclusion criteria will include left or right ventricular assist device implantation or explantation, procedures not requiring cardiopulmonary bypass, active infection or sepsis, severe hepatic disease or ascites, pre-operative renal dysfunction including a baseline creatinine equal to or greater than 2.0 mg/dL or requiring dialysis, immunosuppressive medication use (including steroid use), immunodeficiency syndrome, known neurologic or psychiatric disorder, or use of drugs for psychosis.

Number of Subjects

The incidence of renal dysfunction in patients following cardiac surgery has been reported to be anywhere from 21% to 38%.[13, 17, 18] The incidence of delirium after cardiac surgery has been reported over a broad range including 18% to 31%.[2, 14] Assuming a reduction in the incidence of renal dysfunction and delirium of approximately 10%, an appropriate sample size would be approximately 20 patients per group. We will plan to recruit 26 patients in each group.

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. All aspects of care will be as per usual for patients undergoing these operations at The Mayo Clinic. Subjects will be recruited by letter via review of the surgical listing and scheduled for a preoperative appointment to review the study and obtain consent. Randomization will occur via delivery of a sealed envelope by a member of the study staff who is not directly involved with patient care on the morning of surgery to the consultant anesthesiologist assigning the patient to the ketamine or propofol group.

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 caries. 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 investigators authorized by the IRB will be allowed access to the study data.

Protocol/Methods

After written, informed consent is obtained the following baseline cognitive function studies will be administered by the anesthesia clinical research unit: Trail-making test, the Mini-Mental State Examination, Hopkins Verbal Learning Test (Revised forms 1 and 2), Digit Span forward and backward, Controlled Oral Word Association, and Stroop Test.

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 versus. Maximum fentanyl bolus dosing will be 10 μg/kg, consistent with the currently implemented cardiac surgery rapid recovery protocol. 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. Propofol or dexmedetomidine infusions will be utilized for sedation at the end of the procedure as per usual practice.

The Confusion Assessment method for the ICU (CAM ICU) score will be recorded every 12 hours in the ICU as per routine. After dismissal from the ICU, a CAM score will be reviewed until hospital discharge. Prior to hospital discharge or within 1- 2 days prior to discharge, the patient will undergo post-intervention cognitive function studies administered by the anesthesia clinical research unit: Trail-making test, the Mini-Mental State Examination, Hopkins Verbal Learning Test (Revised forms 1 and 2), Digit Span forward and backward, Controlled Oral Word Association, and Stroop Test.

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 medication record.

Our primary outcomes will be the incidence of cognitive dysfunction and delirium as well as the incidence of renal dysfunction. Secondary outcomes will include assessing differences in hemodynamics, inotropic use and vasopressor use between the ketamine and propofol group. Mortality during admission for cardiac surgery will be assessed, however, the study will not be powered for this to be a primary outcome measure.

Data Analysis

Incidence of renal and cognitive dysfunction and delirium 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.

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