BIOMEDICAL RESEARCH PROTOCOL
UNIVERSITY OF MISSOURI

Project Title: Evaluation of brain and peripheral metabolic and inflammatory markers in patients undergoing open-heart surgery – a pilot study.
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Clinical Trial Phase: N/A

Background & Research Aims

Postoperative cognitive decline (POCD) is a neurological condition following coronary artery bypass grafting surgery (CABG) that occurs in up to 50% of elderly individuals [1,2]. There is considerable clinical variability in POCD, e.g., while the mean duration is typically 4 days, severe cases can persist for months or even into years [3,4]. With POCD being a debilitating and costly problem for older patients[1,2,4–8], there is a need for more effective preventative and interventional measures[4,9–11]. However, with many potential contributing factors for a given patient, it is unknown why and how the anesthetic and surgical procedures induce POCD. Currently, the literature suggests that at least two possible overlapping paths contribute: (A) mitochondrial dysfunction with apoptosis and (B) neuroinflammation. In (A), many rodent studies have found a molecular and behavioral link between inhalational anesthesia, neuronal apoptosis, and cognitive deficits [3,4]. This pre-clinical model is hard to identify in a diverse human clinical group; however, it is clear that many human imaging studies have identified markers of brain health (e.g., measures of whole brain gray matter, decreased functional connectivity) that influence the likelihood of POCD, consistent with the notion that patients with pre-existing cerebral dysfunction will be more sensitive to mitochondrial injury and apoptotic effects from surgery[12–16]. For (B), many studies also link surgical trauma with increased cytokine release, oxidative stress, increased blood brain barrier permeability, and microglial activation. In this hypothesis, additional cerebral injury is propagated directly from the neuroinflammation occurring because of surgery. Together, these two hypotheses (inflammation B and mitochondrial dysfunction A) may overlap, given the links between neurodegenerative disorders with neuroinflammation [8].

We will test the hypothesis that the 7T MR studies acquired in pre-operative patients (n=20) will be informative towards predicting who may develop POCD. We believe that spectroscopic studies of brain health taken in key regions of the brain (hippocampus, frontal lobe), along with peripheral cytokine concentration measurement, may provide additional key biomarker data to personalize this prediction. These data will be compared with data from non-surgical controls thus leveraging our existing data for this project. The primary outcome measure for this study is

the incidence of POCD, assessed by: Mini-Cog score, Confusion Assessment Method (CAM) and hospital stay days.

Recruitment Process

Patients will be identified in collaboration with cardiothoracic surgery team prior to attending preoperative cardiothoracic surgery clinic. Patients will be screened against the inclusion/exclusion criteria and informed about the study by the cardiothoracic surgery team. More detailed screening will be done, using the electronic medical record, by the research team. Should a patient express interest in the study, the research team will approach the patient in the cardiothoracic surgery clinic to obtain written informed consent.

Consent Process

Patients will be approached in cardiothoracic surgery clinic to obtain written informed consent. Patients will be screened for MRI compatibility during the consent process, using the standard MRI safety questionnaire from the Department of Radiology. The study will be explained in full, and all questions will be answered. Patients will be able to choose who is in the room with them, have ample time to consider participation and discuss with family and friends prior to consenting.

Inclusion/Exclusion Criteria

Inclusion criteria:

- Age ≥ 60 years old
- Undergoing elective on-pump coronary artery bypass grafting (CABG) surgery with/without valve repair/replacement.
- Mini-Cog score >4 at baseline.
- Negative for delirium on the CAM at baseline.

Exclusion criteria (general):

- Pre-existing diagnosis of dementia, Alzheimer's Disease, Parkinson’s Disease.
- Emergent CABG ± valve surgery.
- Patients already hospitalized for CABG ± valve surgery.
- Patients using GLP-1 agonists.
- Inability to provide written, informed consent in English.
- Patients who cannot tolerate the KD.
- Patients with alcoholism.
- Patients with liver failure.
- Patients with uremia.
- Mini-Cog score <4 at baseline.
- Positive for delirium on the CAM at baseline.

Exclusion criteria (MRI/MRS):

- Claustrophobia
- Patients with any metal in their body.
- Patients with pacemakers/internal defibrillators/neurostimulators.
- Patients who have any form of stents.

Number of Subjects

Twenty (n=20) patients will be recruited for this pilot study.

Study Procedures

This is a prospective, single center, pilot study.
We target studying n=20 patients. Patients will be approached for written, informed consent during their preoperative cardiothoracic surgery clinic. Once consent has been obtained, patients will be screened with Mini-Cog, a global cognition assessment, and the Confusion Assessment Method (CAM), a screening tool for delirium. Patients who score <4 on the Mini-Cog and/or positive for delirium will be excluded. Patients will also be screened with the MRI safety questionnaire, and any exclusions noted on the safety questionnaire will result to exclusion from the study. The patient will be asked to pre-operatively (within 10 days of surgery) visit the NextGen Imaging facility for MRI/MRS scanning. We will acquire 7T MR spectroscopic studies in the hippocampus and prefrontal cortex (PFC) before surgery. The assessment of neurometabolism will include n-acetyl aspartate (NAA), creatine, glutamate (GLU), glutamine (GLN) and in the KD group, β-hydroxybutyrate (BHB). The MRI/MRS scanning session will have a duration of approximately one hour. During this visit, as well as during surgery and on postoperative day 2, peripheral blood will be drawn to measure peripheral cytokine and ketone concentrations (research-only procedures). On the day of their surgical procedure and post-operative day 2, patients will undergo the Mini-Cog and CAM evaluations.

A research team member will be assigned to each patient, to ensure continuity and rapport.

Post-operative management and procedures:
After CABG surgery, the study team will repeat the Mini-Cog and CAM daily for three days postoperatively, or until delirium resolves. Blood will be drawn via peripheral venipuncture on postoperative day 2 to assess ketone and cytokine concentrations. Patients will be followed until delirium resolves, or until discharge, whichever occurs first.

Potential Risks/Adverse Events

Blood draws may cause pain at the needle site, and potentially slight bruising afterwards. All efforts will be made to coincide study blood draws with clinical blood draws to minimize the number of needle sticks.

MRI/MRS scanning is considered low-risk, however, patients who undergo MRI/MRS scanning may experience headache, nausea, dizziness, and body fatigue from lying in one position for an hour. Side effects from MRI/MRS scanning are rare, and treated symptomatically if it occurs.

There is a small risk of loss of confidentiality, however, all steps will be taken to minimize this risk. All patient-related data will be access controlled and limited to individuals listed on the IRB.

Anticipated Benefits

Patients may not benefit from participation in this study.

The study will indirectly benefit society as it will aim to fill a gap in current medical knowledge about mitochondrial dysfunction, apoptosis, and neuroinflammation of POCD after CABG surgery and may help identify what imaging measures can predict POCD.

Compensation

Patients who complete the pilot study will be compensated $150 ($75 for completion of the imaging day and $75 for completion of the in-hospital part). Gift cards will be given upon completion of the imaging day and upon discharge from hospital. A patient will be eligible for compensation for completing part of the research activities, i.e. should a patient withdraw on the imaging day, they will still be compensated for that day ($75), but not for the in-hospital part.

Costs

There will be no costs incurred to patients in relation to participation in the study.

Data Safety Monitoring Plan

All study-related electronic data will be kept in an access-controlled folder on the University of Missouri's OneDrive. Only individuals registered on this study with the IRB will have access to these data. Paper records will be kept in a fire-safe, access-controlled cabinet. Data will be de-identified to ensure patient confidentiality.

Adverse events, protocol deviations, and other unanticipated problems will be reported by either the principal investigator or the co-investigators to the IRB within 5 business days. Unanticipated deaths will be reported to the IRB within 1 business day.

References/Appendices

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