Project: MADCO-PC Study (Markers of Alzheimer's Disease and Cognitive Outcomes after Perioperative Care
Clinicaltrials.gov registration Number: NCT01993836
Date: July 15, 2016
Document: MADCO-PC Protocol Brief Summary 7-12-2016

MADCO-PC Protocol Summary

Purpose:

This study will examine the hypothesis that changes in the cognition (i.e. thinking and memory) after anesthesia and surgery are correlated with changes in markers of Alzheimers Disease in the fluid around the brain and spinal cord (i.e. cerebrospinal fluid, or CSF), and/or changes in brain connectivity. The investigators will also examine whether different types of anesthesia have different effects on these CSF markers of Alzheimers disease, or different effects on thinking and memory after anesthesia and surgery, or differential effects on the correlation between cognitive changes and CSF marker changes.

Outcome Measures:

Primary Outcome Measure: Assess the correlation between perioperative change in CSF Markers of Alzheimers Disease and perioperative cognitive change. [Time Frame: up to 6 weeks]

We will assess the magnitude of the Spearman correlation coefficient for the relationship between perioperative change in CSF Markers of Alzheimers Disease and the perioperative change in the continuous cognitive index score.

Secondary Outcome Measures:

1. Continuous cognitive index score change [Time Frame: 1 year]

We will examine the difference in the continuous cognitive index score over time in the subjects treated with propofol versus those treated with isoflurane, and versus such changes seen in non-surgical controls. We will also assess the correlation between perioperative change in CSF Markers of Alzheimers Disease and perioperative cognitive change in patients randomized to receive isoflurane vs propofol.

2. Assess CSF Markers of Alzheimers Disease [Time Frame: up to 6 weeks]

We will examine CSF Markers of Alzheimer's Disease over time in the subjects treated with propofol versus those treated with isoflurane, and versus any such changes seen in non-surgical controls.

3. Acute Perioperative CSF Tau/Abeta ratio change [Time Frame: 24 hours]

We will measure the perioperative change in the CSF tau/Abeta ratio from the start of anesthesia/surgery to 24 hours later, and compare this to changes seen in the non-surgical controls at the cognate time points.

4. Chronic Perioperative CSF Tau/Abeta ratio change [Time Frame: 1 year]

We will measure the stability of any acute 24 hour postoperative changes in the CSF tau/Abeta ratio out to 6 weeks and 1 year later in surgical patients, and compare these changes to any changes seen over time in the non-surgical controls.

Enrollment Numbers, Inclusion and exclusion criteria

Targeted enrollment is 108 surgical patients who complete the 6 week follow up visit, which provides >80% power to detect a spearman correlation coefficient of 0.3 or greater (a low-

moderate correlation) for the aforementioned primary outcome measure. 54 non-surgical controls will also be enrolled as described below.

Ages Eligible for Study: 60 Years and older

Genders Eligible for Study: Both

Inclusion Criteria:

- Age 60 year or older
- Surgery scheduled to last at least 2 hours (including time for anesthesia induction, etc)
- English speaking ability.

Exclusion Criteria:

- Inmate of a correctional facility (i.e. prisoners).
- Pregnancy
- Documented or suspected family or personal history of malignant hyperthermia.
- Patient unable to receive either propofol or isoflurane due to allergy or other specific contraindication.

Inclusion criteria for the non-surgical controls are the same as those described above, with the exception of the second inclusion criteria (surgery scheduled to last at least 2 hours). Non-surgical controls (i.e. community dwelling older adults) will be recruited from several Duke research subject registries, and will be matched to surgical patients on a 2:1 basis (2 surgical patients for each non-surgical control) based on age, sex, and educational status. Non-surgical controls will undergo the same study procedures as surgical patients at the same cognate time intervals.

Study Procedures:

Cognition: Our full POCD cognitive test battery (as described in Newman MF et al, NEJM, 2001) is performed on study patients within one month (typically one week) prior to anesthesia and surgery, and then again six weeks and one year after anesthesia and surgery.

All patients are screened for delirium on postoperative days one through seven by our experienced neurocognitive testing team.

Biochemical Studies/Samples: CSF and peripheral blood samples are obtained immediately prior to anesthesia and surgery, 24 hours later, six weeks later, and one year later. These samples will be assayed for Alzheimer's disease biomarkers (including amyloid beta, tau and phospho-tau) as well as inflammatory markers and other biomarkers of interest.

Brain imaging: Functional MRI scans are performed within one month prior to Anesthesia and surgery, and then again six weeks after anesthesia and surgery. Multiple scan sequences are used to evaluate anatomic and functional Brain connectivity.

For more information, please see:
https://clinicaltrials.gov/ct2/show/NCT01993836?term=Miles+Berger&rank=1

Newman MF et al, *NEJM*, 2001.
Berger M et al, *Anesthesiology Clinics*, 2015.
Berger M et al, *JCTVA*, 2014.