Project: MADCO-PC Study (Markers of Alzheimer's Disease and Cognitive Outcomes after Perioperative Care

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Statistical Analysis Plan

ACTIVATE: CSF trajectories

SAP Version: 5.0

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Author: Mary Cooter

Primary Investigator: Miles Berger

Revisions/Notes:

V2.0 5/20/17: Revised SAP structure to highlight hypotheses of interest, added data flow diagram and table shell

V3.0 6/5/17: Made primary and secondary hypotheses to match order in ct.gov listing. Added in current table 1

V4.0 7/28/17: There are 2 patients whose CSF data has yet to be analyzed, currently analyzed with imputation but if results returned from the lab will want to incorporate that data into the analysis.

Study Objective: AD biomarker change in CSF and relationship with cognitive change.

Animal studies have shown that inhaled anesthetic agents increase the levels of Alzheimer's disease related neural markers (such as amyloid beta and tau). Several studies have measured blood serum markers indirectly related to Alzheimer's disease in patients randomized to inhaled versus intravenous anesthesia, no randomized controlled trial has ever examined these markers in the cerebrospinal fluid of patients given inhaled versus intravenous anesthesia. No randomized controlled study to date has ever examined whether inhaled anesthetics (versus intravenous anesthetics) alter brain levels of Alzheimer's associated markers in humans, and/or whether such changes (if they occur) correlate with POCD or other cognitive changes, or changes in brain structure or activity after surgery and anesthesia.

Here, we propose to measure Alzheimer's disease-related neural markers in the cerebrospinal fluid (CSF) of patients exposed to anesthesia during surgery, as well as in non-surgical controls (age matched community dwelling individuals age 60 and over). These studies should clarify the effect of common anesthetic agents on Alzheimer's disease related neural markers and cognitive outcomes.

1. Hypotheses:
    i. The degree of increase in AD marker CSF levels will be associated with cognitive outcomes.
    ii. AD biomarkers will increase from baseline to the 24 hours postop time point.
2. Outcomes:

Outcome	**Description**	**Specifications**	**Variables and Source**
Cognitive Change from baseline to 6 weeks	As a numeric variable (continuous cognitive change) or as binary outcome (POCD w/>1 or 2 SD drop)	Derive factor weights within sample and compare to that of historical non-cardiac population	Use bluecap database for cognitive data

3. Study population and datasets:

Inclusion Criteria: Patients undergoing urologic, general or other surgical procedures, aged 60 and above, English speaking **[Per PI will include all patients with BL and 6 week cognitive data available and run imputations to fill in missing CSF data in primary analysis]**

Exclusion Criteria: inmate of a correctional facility (i.e. prisoners), documented or suspected family or personal history of malignant hyperthermia, unable to receive either propofol and/or isoflurane due to allergy or other specific contraindication, receiving systemic chemotherapy after the first cognitive testing session and before the 6 wk or 1 year follow up cognitive testing sessions, major head trauma that occurs after the first cognitive testing session and before the 6 wk or 1 year follow up cognitive testing sessions.

Data Set Sources

Penn AD CSF data— Contains baseline, 24hr, and 6 week AD biomarker analysis (tau, abeta, p-tau)
Patient characteristics data—IT pull ticket 2494
Cognitive Data--Use BlueCap database and data entry from CRC groupAD Biomarkers (Primary Variable of Interest)

Variable names	Description	Specifications (e.g. formula)
CSF A beta	Measured BL, 24 hr, 6 weeks	Look at individual time points, trajectory, and change BL to 24 hr, and BL to 6 weeks
CSF tau		
CSF phospho-tau		
CSF tau/a beta	Quotient of tau and a-beta at each time point	
CSF p-tau/a beta	Quotient of p-tau and a-beta at each time point	

4. Adjustment Variables

Candidate Covariates	Description
Anesthetic Type (randomized)	Propofol vs. Isoflurane group
Demographics	age, BMI, race, sex, years of education
Baseline Cognitive Status	MMSE score (raw and categorical [≥25, 20-24, <20]), mean cognitive index, domain scores
Clinical Factors	ASA status, surgical type (urology, orthopedics, plastics, thoracic surgery, general/abdominal, gynecologic etc), open incision vs laparoscopic approach, epidural block, regional block, vs no block, surgery duration (from incision to end surgery time stamps), IO BIS (mean of median filtered), ET aaMAC (mean of medians filtered), propofol dose, ketamine use, dexmedetomidine use, admitted to ICU by POD1

6. Statistical Methods and results

0. Merge, clean summarize data and check missing-ness patterns and tabulate data
    i. Merge demographic data from IT pull, the Penn CSF data, and bluecap cognitive data
    ii. Summarize numeric (mean (SD), median [Q1, Q3]) and categorical (N (%)) patient Characteristics.
        a. Will look across anesthetic type and compare characteristics between types
        b. Will use standardized differences to assess group differences (if required will add p-values from univariable tests of association (t-tests, WRS, chi-square, or Fisher's Exact)

ii. Calculate degree of missingness (expected to be 10% or less)
    a. Determine if missingness is sufficiently random or if highly correlated with specific values
    b. Develop imputation strategy for CSF and cognition—SRCWare
        i. Used the following variables for imputation: age weight height years education, gender, race, ASA, surgical service, iso vs prop group, surgery duration, baseline MMSE, and available baseline, 24hr and 6 week CSF and nptest data

iii. Determine how cognitive factors will be calculated
    a. Using same sample for derivation of factor loadings and analysis
        i. Performed factor analysis and wrote code to evaluate stability of the solution (code factorsolutionchecking.sas)
        ii. Determined that solution from ACTIVATE cohort is too unstable to use
        iii. Emailed with PI and per emails on 7/27 will proceed with using historical weights
    b. Using historical sample weights
        a. Re-ran factor analysis on ND sample (N=389) to get oblique solution
        b. Code applied in impute_data.sas, based on McDonagh et al datasets

Hypothesis 1: The degree of increase in AD marker CSF levels will be associated with cognitive outcomes.

1. Data visualization of
    a. differences in 24 hour and six-week CSF change and numeric/binary cognitive outcomes (figure 2)—ACTIVATE _ResultsSummary_0727 sheet CSFTraj_byPOCD and CSFchange
    b. Added 7/28/17: Spaghetti plots of individual change over time
    c. Added 7/28/17: Use of Les Shaw cut points for MCI/AD, and four quadrant plot of observed Tau by AB---—Based on Miles' personal correspondence (7/28) with Les he recommended the same threshold for Tau (93), but an increased Abeta cutoff of 250.
2. Univariate Analysis
    a. Association of CSF change with numeric cognitive outcome via correlation coefficient (Pearson/spearman)--- ACTIVATE _ResultsSummary_0727 sheet CSFchange
    b. Association of CSF change with binary cognitive outcome via t-tests or Wilcoxon rank sum tests.
        i. Summary statistics on ACTIVATE _ResultsSummary_0727 sheet CSFchange
        ii. Still need to determine how to run non-parametric test on MI datasets (as of 7/28)
    c. Added 7/27/17: Association of baseline CSF with numeric baseline cognition and cognitive change via spearman correlation
3. Multivariate Analysis
    a. Use linear and logistic regression to study association of CSF with cognition adjusting for patient characteristics
    b. Candidate variables for model: age, ASA status, years of education, baseline cognitive index, baseline MMSE score, baseline CSF AD biomarker measures, CSF AD biomarker changes from before to after surgery (from before to 24 hrs postop, and from before to 6 weeks postop), DARS, mean of median end tidal MAC fraction (age adjusted), surgery type, surgery length, MAC-hours, cumulative propofol dosage
    c. Adjustment variables added as indicated via univariate association with outcome and as allowed by sample size restrictions in model

d. Model assumptions will be evaluated and performance measured
    i. Numeric cognitive change: assess residual Q-Q plot, mse, R2
    ii. Binary cognitive change: C-index, R2, GOF

4. Investigate CSF associations with individual cognitive domains in exploratory analysis (figure 3). This would help evaluate for the possibility that pre to post op changes in CSF AD biomarkers may be particularly related to changes in one particular cognitive domain (such as memory) rather than global cognition.

Hypothesis 2: AD biomarkers will increase from baseline to the 24 hours postop time point.

1. Data visualization of CSF change over time (BL, 24hrs, 6wk)—Figure 1
2. Calculate change from baseline to
    a. 24 hrs—assess if change is significant via t-test or Wilcox Signed Rank Test
    b. 6 week—assess if change is significant via t-test or Wilcox Signed Rank Test
3. CSF trajectory analysis (BL, 24hr, 6 week)—repeated measures mixed model

7. Proposed Tables and Figures

1. Table 1 describing baseline characteristics of the study cohort
    a. Demographics: age, BMI, race, sex, years of education
    b. Baseline Cognitive status: MMSE score (raw and categorical [≥25, 20-24, <20]), mean cognitive index, domain scores
    c. Baseline CSF measures
    d. Clinical factors: ASA status, surgical type (urology, orthopedics, plastics, thoracic surgery, general/abdominal, gynecologic etc), open incision vs laparoscopic approach, epidural block, regional block, vs no block, surgery duration (from incision to end surgery time stamps), IO BIS (mean of median filtered), ET MAC (mean of medians filtered), propofol dose, ketamine use, dexmedetomidine use, admitted to ICU by POD1

2. Figure 1
    a. CSF A beta as a function of time- preop, 24 hr postop, 6 weeks postop
    b. CSF tau as a function of time- preop, 24 hr postop, 6 weeks postop
    c. CSF phospho-tau as a function of time- preop, 24 hr postop, 6 weeks postop
    d. CSF tau/a beta ratio as a function of time- preop, 24 hr postop, 6 weeks postop
    e. CSF p-tau/a beta ratio as a function of time- preop, 24 hr postop, 6 weeks postop
    f. (Could also consider making stratified plots for 2A-2D with two lines for each graph, one line for patients with POCD by either a 1 or 2 SD drop in any cognitive domain rule, and one line for patients without POCD)

3. Figure 2
    a. Dot plot- CSF tau change from preop to 24 hrs on Y axis, Continuous Cognitive index change from before to 6 weeks on X axis, each patient is one dot on the graph
    b. Dot plot- CSF tau change from preop to 6 weeks on Y axis, Continuous Cognitive index change from before to 6 weeks on X axis, each patient is one dot on the graph;

c. (or could combine plots 3A and 3B by just plotting maximal increase in CSF tau from preop to either 24 hrs or 6 weeks on Y axis- whichever is larger- and cognitive change index from preop to 6 weeks postop on X axis)
d. C, D- equivalent of 2a,2b, but with amyloid beta instead of tau
e. E, F- equivalent of 2a,2b, but with p-tau instead of tau
f. G Dot plot- CSF tau/abeta ratio change from preop to 24 hrs on Y axis, Continuous Cognitive index change from before to 6 weeks on X axis, each patient is one dot on the graph;
g. H Dot plot- CSF/Abeta tau ratio change from preop to 6 hrs on Y axis, Continuous Cognitive index change from before to 6 weeks on X axis, each patient is one dot on the graph;

4. Repeating Figure 2 A-D with the X axis representing change in each of the 4 individual cognitive domain scores rather than the overall cognitive index score.