The INTUIT Study: Investigating Neuroinflammation Underlying Postoperative Cognitive Dysfunction

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BACKGROUND/OBJECTIVES: Every year, up to 40% of the more than 16 million older Americans who undergo anesthesia/surgery develop postoperative cognitive dysfunction (POCD) or delirium. Each of these distinct syndromes is associated with decreased quality of life, increased mortality, and a possible increased risk of Alzheimer's disease. One pathologic process hypothesized to underlie both delirium and POCD is neuroinflammation. The INTUIT study described here will determine the extent to which postoperative increases in cerebrospinal fluid (CSF) monocyte chemoattractant protein 1 (MCP-1) levels and monocyte numbers are associated with delirium and/or POCD and their underlying brain connectivity changes.

DESIGN: Observational prospective cohort.

SETTING: Duke University Medical Center, Duke Regional Hospital, and Duke Raleigh Hospital.

PARTICIPANTS: Patients 60 years of age or older (N = 200) undergoing noncardiac/nonneurologic surgery.

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[Corrections added January 25, 2019, after first online publication. INTUIT study investigators were updated from Dele Erdmann, David Harpal Jr, and Laura Harley to Detlev Erdmann, David Harpole Jr, and Laura Havrilesky. Jennifer H. Enzor and Janet Staats were added to the list of INTUIT study investigators. James Deorio should was updated to James K. DeOrio. Thomas Bunning was updated from BA to BS. An MA was included for Charles M. Giattino. ††was updated from Department of Psychology and Neuroscience, Duke University Medical Center, Durham, North Carolina to Department of Psychology and Neuroscience, Duke University, Durham, North Carolina. Additional gratitude was expressed in the acknowledgments section.]

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MEASUREMENTS: Participants will undergo cognitive testing before, 6 weeks, and 1 year after surgery. Delirium screening will be performed on postoperative days 1 to 5. Blood and CSF samples are obtained before surgery, and 24 hours, 6 weeks, and 1 year after surgery. CSF MCP-1 levels are measured by enzyme-linked immunosorbent assay, and CSF monocytes are assessed by flow cytometry. Half the patients will also undergo pre- and postoperative functional magnetic resonance imaging scans. 32-channel intraoperative electroencephalogram (EEG) recordings will be performed to identify intraoperative EEG correlates of neuroinflammation and/or postoperative cognitive resilience. Eighty patients will also undergo home sleep apnea testing to determine the relationships between sleep apnea severity, neuroinflammation, and impaired postoperative cognition. Additional assessments will help evaluate relationships between delirium, POCD, and other geriatric syndromes.

CONCLUSION: INTUIT will use a transdisciplinary approach to study the role of neuroinflammation in postoperative delirium and cognitive dysfunction and their associated functional brain connectivity changes, and it may identify novel targets for treating and/or preventing delirium and POCD and their sequelae. **J Am Geriatr Soc 67:794–798, 2019.**

Key words: neuroinflammation; monocyte; monocyte chemoattractant protein 1; postoperative cognitive dysfunction; delirium

More than 16 million older Americans undergo anesthesia/surgery every year,[1] and up to 40% may develop postoperative cognitive dysfunction (POCD)[2,3] or delirium.[4] POCD (also termed neurocognitive disorder-postoperative when accompanied by subjective cognitive complaints) is generally defined as a drop in cognitive performance of 1 to 2 or more standard deviation(s) (SDs) that occurs more than 1 month after surgery, as compared with preoperative cognitive testing.[5] Although delirium and POCD are distinct disorders, both are associated with decreased quality of life (QOL),[6] increased mortality,[7] and a possible increased risk for developing dementia, such as Alzheimer's disease (AD).[8]

One pathologic process that may underlie POCD, delirium, and AD is neuroinflammation.[2,8,9] Several studies have shown higher proinflammatory cytokine levels in serum[10] and cerebrospinal fluid (CSF)[9–11] of patients with postoperative delirium, POCD, and/or AD.[12] CSF MCP-1 levels and monocyte numbers increase from 1 hour before to 24 hours after surgery/anesthesia.[10,13,14] In a pilot study, we found that CSF monocyte MCP-1 receptor expression decreased 24 hours after surgery in patients who later developed POCD, suggesting that increased monocyte chemoattractant protein 1 (MCP-1) levels induce monocyte influx into the central nervous system and monocyte MCP-1 receptor downregulation.[13]

Neuroinflammation can also alter connectivity in the default mode network (DMN), a set of functionally connected brain regions identified by functional magnetic resonance imaging (fMRI).[15–17] Altered DMN connectivity has been observed in patients with AD,[15,17] delirium,[18] and POCD.[19] This study, Investigating Neuroinflammation Underlying Postoperative Brain Connectivity Changes, Postoperative Cognitive Dysfunction, Delirium in Older Adults (INTUIT), will further investigate the relationship between increases in CSF MCP-1 levels and monocyte numbers, and changes in DMN connectivity in patients with POCD and delirium (Figure 1).

Increased CSF MCP-1 levels and monocyte brain influx have also been associated with AD progression.[10,20] We recently demonstrated that neuroinflammation magnitude (as measured by CSF MCP-1 levels) is associated with postoperative increases in the CSF AD biomarker tau after neurosurgery.[14] CSF tau levels also increase after cardiac[21] and orthopedic[22] surgery. The INTUIT study will use CSF assays, fMRI, electroencephalography (EEG), cognitive testing, and delirium screening to investigate relationships between postoperative neuroinflammation and POCD, delirium, CSF AD biomarker changes, and altered DMN connectivity in older adults.

METHODS

Overview

INTUIT is an ongoing 5-year observational prospective cohort study and has thus far enrolled 91 patients. Participants undergo pre- and postoperative cognitive testing and delirium screening, QOL assessments, fMRI scans, intraoperative EEG recordings, and CSF and blood analyses. Each subject is followed for 1 year. Table 1 shows the timeline of activities for study subjects.

Eligibility

We will enroll 200 English-speaking adults 60 years or older undergoing noncardiac/nonneurologic surgery scheduled for 2 hours or longer at Duke University Medical Center, Duke Regional Hospital, and Duke Raleigh Hospital. Anticoagulation precludes most cardiac surgery patients from undergoing lumbar punctures, hence their exclusion. Patients who complete cognitive testing and blood/CSF sampling at all study time points will count toward the enrollment target. A total of 100 patients will also undergo pre- and postoperative MRI/fMRI.

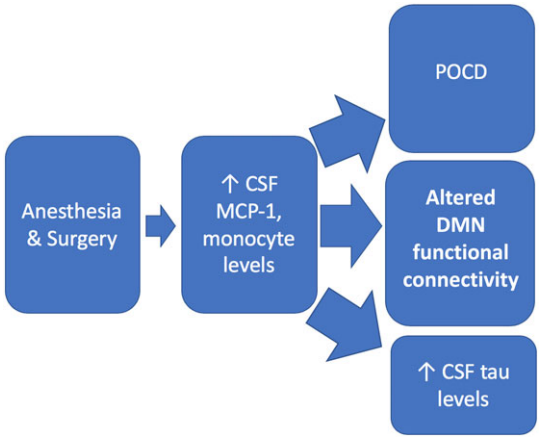

Figure 1. Conceptual framework for the INTUIT study. This study will assess potential associations between postoperative increases in cerebrospinal fluid (CSF) monocyte chemoattractant protein 1 (MCP-1) and monocytes and postoperative cognitive disorder (POCD), default mode network (DMN) functional connectivity changes, and increased CSF tau protein levels that could suggest a link between POCD and Alzheimer's disease progression.

Table 1. Activities and Timeline for INTUIT Participants

	0-2 wk before surgery	0-1 h before anesthesia/surgery	During surgery	24 h after anesthesia/surgery	Daily until hospital discharge	6 wk after surgery	1 y after surgery
Cognitive testing	X					X	X
Physical function, QOL assessments	X					X	X
fMRI scans	X					X	
EEG		X	X				
Delirium screening	X	X		X	X	X	
CSF and blood sample collection		X		X		X	X

Abbreviations: CSF, cerebrospinal fluid; EEG, electroencephalography; fMRI, functional magnetic resonance imaging; QOL = quality of life.

There are no preoperative cognitive status exclusions. The following are not eligible: (1) patients on immunosuppressants (eg, steroids) or immunomodulatory therapy, chemotherapeutic agents with known cognitive effects, or anticoagulants that would preclude safe lumbar punctures; (2) inmates of correctional facilities; and (3) patients who experience major head trauma or receive chemotherapy between the baseline and either postoperative cognitive testing session. Patients with MRI contraindications will not undergo MRI/fMRI.

The INTUIT study was approved by the Duke University Health System institutional review board and is registered with clinicaltrials.gov (NCT03273335). Written informed consent is obtained from all participants or their legally authorized representative before study participation.

Study Assessments and Schedule

Cognitive Testing

POCD is assessed with a standard cognitive test battery (Table 2)[3,23] by staff trained by a board-certified neuropsychologist; the full test battery takes approximately 30 to 60 minutes to complete. Individual test scores are combined by factor analysis into four cognitive domains: verbal memory, executive function, attention and concentration, and visual memory.[3] The mean of these domain scores yields the Continuous Cognitive Index (CCI), a sensitive score used to quantify overall cognitive function. CCI change from before to after surgery thus quantifies the degree of learning or cognitive decline.[3] POCD as a dichotomous outcome is defined as an SD drop of 1 or more from before to 6 weeks after surgery in one or more cognitive domain.[3]

Table 2. Cognitive Test Battery[3,19,23]

Test	Assessment
Wechsler Test of Adult Reading[a]	Premorbid intellectual functioning
Mini-Mental Status Examination	Cognitive impairment (orientation, registration, attention and calculation, recall, language)
Wechsler Memory Scale-Revised Modified Visual Reproduction Test	Visual immediate and delayed memory recall
Hopkins Verbal Learning Test	Auditory immediate and delayed memory recall (learning, episodic verbal memory)
Randt Short-Story Memory Test	Auditory immediate and delayed memory recall
Digit Span[a]	Auditory-verbal simple and complex attention
Trail Making Test A and B	Complex executive functioning skills (eg, logical task switching)
Digit Symbol[a]	Visuomotor performance and processing speed
Lafayette Grooved Pegboard Test	Manual dexterity

[a]A subtest of the Wechsler Adult Intelligence Scale-Revised.

Physical and QOL Assessments

Physical function is assessed via Timed-Up-and-Go (TUG)[24] and Romberg tests, Duke Activity Status Index (DASI),[6] Elderly Falls Screening Test,[25] Fall-Risk Screening Test,[26] and the Short-Form-36 Health Survey (SF-36) (including the physical function subscale).[6] QOL and subjective cognitive complaints are assessed as previously described.[6] These assessments occur less than 1 month before and 6 weeks and 1 year after surgery.

Delirium Screenings

Delirium is assessed twice daily after surgery in the hospital. We use the Confusion Assessment Method for the ICU (CAM-ICU) in intubated patients[27] and the 3D-CAM in nonintubated patients.[28] In past studies, the interrater reliability coefficient of our delirium assessors was more than .95. Patients also complete the 3D-CAM at their initial baseline study visit.

EEG Recording

The 32-channel EEG recordings are obtained pre- and intraoperatively as previously described.[29] We also examine whether increased EEG complexity/entropy measures predict postoperative cognitive resilience (ie, lower rates and/or severity of POCD and delirium, or more rapid or complete return to baseline).

Blood and CSF Sampling of Inflammatory Mediators

Blood and CSF are collected before surgery and 24 hours, 6 weeks, and 1 year after surgery via sterile venipuncture and lumbar puncture, respectively, and flow cytometry is used to assess CSF monocytes as described.[13] The monocyte-to-lymphocyte ratio is used to evaluate these two major leukocyte populations in CSF as recently described.[13] CSF supernatant is analyzed using multiplex enzyme-linked immunosorbent assay

(ELISA) to measure levels of the cytokines MCP-1, interleukin (IL)-6, IL-8, and granulocyte colony-stimulating factor (G-CSF).[14]

CSF tau levels are measured before surgery and 24 hours and 6 weeks after surgery at the Alzheimer's Disease Neuroimaging Initiative biomarker core lab[14] that has well-validated multiplex ELISA-based bead assays for CSF tau, phospho-tau, and amyloid-beta levels.[30] To avoid measurement bias, sample measurements are performed in random order, and technicians are blinded to study subject number and time point. To minimize confounding from diurnal variation, CSF samples per patient are collected at the same time of day (± 1 h) whenever possible.

Functional MRI Scans

The fMRI scans will be performed on the first 100 eligible patients within 1 month before and 6 weeks after surgery in a 3-T scanner with an eight-channel head coil.[19] Anatomical scan sequences are high-resolution T1-weighted fast-spoiled gradient-echo oblique axial acquisitions (256 × 256 matrix, 256-mm field-of-view [FOV], 11-degree flip angle, 136 1-mm-thick slices, TR/TE, 6.93/3.0 ms), and T2 fluid-attenuated inversion recovery oblique axial acquisitions (128 × 128 matrix, 256-mm FOV, 90-degree flip angle, 68 2-mm-thick slices, TR/TE, 2250/11 000 ms, inversion time 2250 ms).[19] The two resting-state fMRI sequences are sensitivity-encoding, spiral-in, oblique, axial, slice-interleaved acquisitions (64 × 64 matrix, 256-mm FOV, 60-degree flip angle, 34 4-mm-thick slices, TR/TE 3000/30 ms, sensitivity-encoding factor 2).[19] The first 18 seconds of each resting-state fMRI sequence is discarded to correct for initial MR signal fluctuation. Data from the next 124 time points (6.2 min) is retained for functional connectivity analysis. To minimize head motion during scans, we use a firm head rest and instruct participants to remain still.

The fMRI scans focus primarily on predefined regions of interest in the DMN and salience network. Based on our pilot data, we expect increases in CSF MCP-1 and monocyte-to-lymphocyte ratio from before to 24 hours after surgery to predict altered inter-network resting-state connectivity between the anterior to posterior cingulate from before to 6 weeks after surgery.[19] Anatomical and perfusion MRI sequences allow us to account for effects of potential fMRI data confounders and to facilitate additional analyses.

Sleep Apnea Testing

In the nested Sleep Apnea, Neuroinflammation, and Dysfunctional Cognition Manifesting After New Elective Surgery (SANDMAN) cohort substudy, the first eligible 80 INTUIT patients (ie, those not already on home continuous positive airway pressure therapy) will undergo preoperative home sleep testing to measure sleep apnea severity (apnea-hypopnea index [AHI]). Multivariate analysis will determine the extent to which AHI is associated with POCD severity and/or CSF cytokine levels.

Data Management

Each study subject is assigned a unique ID number, different from his or her hospital ID number. All data and subsequent analyses are stored securely under this unique ID without patient identifiers.

Statistical Analysis

Based on prior studies,[3,23] we expect a completion rate more than 75% and a POCD incidence of approximately 40% at 6 weeks after surgery. With $\alpha = 0.05$, a 150-patient study will provide more than 90% power in a 2-sided *t* test to detect a larger increase (Cohen's d = 1.07) in the CSF monocyte-to-lymphocyte ratio from before to 24 hours after surgery in patients who later develop POCD at 6 weeks after surgery. Enrollment of 200 patients will ensure that at least 150 patients complete the 6-week visit (Table 1). Based on preliminary data demonstrating an approximately 50% incidence of postoperative CSF MCP-1 increases, and $\alpha = 0.05$, a 150-patient study will also provide more than 90% power to detect worse postoperative cognitive function (Cohen's d = 0.5), as measured by the CCI change from before to 6 weeks after surgery in patients with increased postoperative CSF MCP-1 levels. After univariate *t* tests, we will perform multivariate linear and logistic regression analyses of continuous and dichotomous cognitive outcomes, respectively, to account for dependencies between MCP-1 and monocytes, adjust for potential confounders that may contribute to POCD, delirium, and/or dementia,[2–4,8] and predict outcomes in future patients.

We previously found a correlation coefficient (R) of 0.57 between CSF MCP-1 and tau increases from before to 24 hours after surgery in neurosurgery patients,[14] although this correlation may be smaller in nonneurosurgery patients. A 150-patient study will provide more than 90% power to detect $R \geq 0.3$ (a low moderate correlation) between CSF tau and MCP-1 levels after surgery, as well as changes between CSF monocyte-to-lymphocyte ratio and CSF tau levels before and after surgery. Postoperative tau change is nonnormally distributed[30] and thus requires nonparametric analysis.

Our preliminary (unpublished) data show a 5% normalized change in anterior to posterior cingulate connectivity per 10 pg/dL change in MCP-1 levels. Thus 100 patients will provide more than 90% power to detect $R \geq 0.3$ and allow regression analyses to quantify the magnitude of change between the CSF monocyte-to-lymphocyte ratio and anterior to posterior cingulate connectivity.

DISCUSSION

INTUIT will assess the association between CSF MCP-1 increases and monocyte-to-lymphocyte ratio changes, brain functional connectivity changes, and AD biomarkers in the pathogenesis of POCD and/or delirium. We expect CSF increases in MCP-1 and monocytes to correlate with increased POCD severity and increased CSF tau levels postoperatively. However, if postoperative increases in CSF MCP-1 levels and the monocyte-to-lymphocyte ratio do not correlate with postoperative increases in CSF tau levels, that would suggest these may be independent processes. Because INTUIT also measures IL-6, IL-8, and G-CSF levels as well as phospho-tau and amyloid-beta levels, we may discover that changes in other proinflammatory cytokines and/or AD biomarkers in the CSF correlate more strongly with POCD.

This work will also inform future studies on aging-related biological processes and postoperative outcomes in

older adults. CSF and blood samples will be obtained before and after known stressors (ie, anesthesia/surgery), allowing determination of the extent to which anesthesia/surgery alters molecular/cellular markers of the aging process, and the potential role of such biomarker alterations in postoperative delirium, cognitive dysfunction, and AD progression in the elderly. Although the aims of this study are focused on neuroinflammatory biomarkers of postoperative delirium and POCD, the data collected will enable investigation of other promising biomarkers and resiliency predictors. For example, the Physical Resiliencies: Indicators and Mechanisms in the Elderly Collaborative (PRIME) study will analyze INTUIT EEG data to determine whether EEG multiscale complexity before and during surgery can predict postoperative cognitive resilience.

In conclusion, the INTUIT study will investigate the association between CSF MCP-1 and monocyte increases, and worsening postoperative cognition, functional brain connectivity changes, and CSF tau increases. These findings are expected to identify potential therapeutic targets for future preventive and/or treatment strategies for delirium and POCD.

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