Post-Operative Cognitive Dysfunction in Normal Aging Patients Undergoing Elective Orthopedic Surgery

Clinical Study Protocol

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Sponsor
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This study will be conducted in compliance with the protocol, IND regulations and other applicable regulatory requirements.

Participant Contact Project Narrative

1. *Summary*

Post-operative cognitive dysfunction (POCD) is a common concern for aging patients undergoing elective orthopedic surgery and significantly effects health outcomes. This study aims to evaluate the incidence of and risk factors associated with post-operative cognitive dysfunction in aging patients without prior history for mild cognitive impairment or dementia. Furthermore, we plan to explore neurofilament light (NfL), a blood biomarker of neuronal injury, to better identify patients pre-operatively at greater risk for dementia and therefore, more likely to experience POCD. This project is intended to 1) foster a better understanding of POCD incidence in patients undergoing elective surgery; 2) identify pre and peri-operative risk factors for POCD; and 3) explore the role of biomarkers such as NfL in predicting POCD.

2. *Study aims*

Primary Aim: Estimate the incidence of post-operative cognitive dysfunction three months after orthopedic surgical intervention.

Secondary Aims:

- Determine pre and peri-operative risk factors associated with development of POCD
- Explore the role of serum neurofiliament light (NfL) in predicting risk for development of POCD

3. *Background, Rationale, Significance*

In neurology clinic, aging patients frequently inquire regarding the risk of cognitive decline following elective orthopedic surgery. These individuals are often faced with the challenging decision of proceeding with surgical intervention while risking potential cognitive decline versus deferring on surgery and enduring the original orthopedic condition justifying the operation.

The term postoperative cognitive dysfunction (POCD) describes a deterioration of cognition that is temporally associated with surgery (Lezak MD Neuropsychological Assessment NY 2004). As opposed to delirium, POCD depends on valid assessments of preoperative and postoperative cognitive function. The underlying etiology of POCD remains unclear. Cerebrovascular disease, cerebral hypoperfusion, genetic susceptibility, alteration in neurotransmitter function, neurohumoral stress, and central nervous system (CNS) inflammatory phenomenon have all been suggested, but the principal suspect has been general anesthesia (Silverstein JH et al Anesthesiology March 2007). However, numerous studies suggest that choice of anesthesia is *not* an important factor in the development of POCD (Wu Reg Anesth Pain Med 2004).

There is an absence of guidelines related to orthopedic surgery and cognitive dysfunction risk to inform the decision-making process for proceeding with surgery in the elderly. The largest trial of POCD was published by anesthesiologists and looked at 1,218 patients aged ≥60 at baseline, 1 week, and 3 months post operatively, finding an overall incidence of 25.8% for cognitive dysfunction (Moller JT Lancet 1998). Increasing age, duration of anesthesia, little education, a second operation, postoperative infections, and respiratory complications were risk factors for early postoperative cognitive dysfunction (1 week post-op), but only age was a risk factor for late postoperative cognitive dysfunction (3 months post-op). Limitations to this study include the fact that results were not limited to a certain type of surgery (eg.

orthopedics) and a MMSE of ≥24 was used to define normal cognition in this population. Currently, the MMSE is seen as an insensitive screening test in which patients with mild dementia may still score within normal limits ≥24 (Lezak MD Neuropsychological Assessment NY 2004).

Since this question of whether POCD is associated with orthopedic surgery has not been extensively investigated in the neurology or orthopaedic literature, we plan to study longitudinal cognitive performance in a cohort of n=100 aging patients undergoing elective hip, knee, and shoulder replacement at Regions hospital. Recruitment will take place over a six month period. Consented patients will receive a cognitive battery consisting of standardized measures of attention, learning, memory, processing speed, and mood at baseline and 3 months. In addition to the incidence of post-operative cognitive dysfunction, demographic and clinical variables related to the surgery (eg. age, anaesthesia, medical complications, etc) will be evaluated to identify risk factors. Variables such as cancer, alcohol abuse, and narcotic use are included for evaluation based on the literature suggesting these pre-disposing risk factors may relate to increased risk of POCD. This data will serve to provide valuable information related to risk of cognitive dysfunction following orthopedic surgery, which will not only benefit neurology providers, orthopedic surgeons, but patients who are themselves making informed healthcare decisions, as well.

In addition, we are interested in the utilization of blood biomarkers as predictive factors of POCD. With central nervous system and peripheral nervous system neuronal injury, the concentration of neurofilament light chain (NfL) has been found to increase in cerebrospinal fluid and blood (Olsson B JAMA Neurol 2018). NfL is a subunit of neurofilaments, which are cylindrical proteins exclusively located in the neuronal cytoplasm, conferring structural stability to neurons. In the setting of inflammatory, neurodegenerative, traumatic, or vascular injury to axons, the release of NfL sharply increases, resulting in detectable levels in the blood and CSF (Disanto G Ann Neurol 2017). A variety of neurological conditions that impact the CNS and cognitive result in elevation of blood and CSF levels of NfL; these include HIV associated dementia, amyotrophic lateral sclerosis, Creutzfeldt-Jakob disease, progressive supranuclear palsy, frontotemporal dementia, Lewy body dementia, and Alzheimer's disease (Gaetani L JNNP 2019). Since NfL is a sensitive, but non-specific marker of axonal injury, it may be an effective tool to distinguish aging patients who are at risk of undergoing pre-operative cognitive decline from those who are experiencing normal aging.

4. *Approach*

a. Study design

This is a prospective, cohort study evaluating cognition at baseline and post-operatively at 3 months in older adults undergoing orthopedic surgery. Any subjects with a history of cognitive impairment or any abnormal cognitive screening result will be excluded from the study. Findings from the cognitive testing will be compared between baseline and 3 months, and participants with a 1.5 SD decrease in any cognitive domain will be considered to have developed POCD. We will then determine pre and peri-operative risk factors associated with development of POCD. Finally, serum studies for NfL will be drawn during the baseline visit.

b. Population

We will be enrolling patients presenting to Regions orthopedics and TRIA Woodbury with a scheduled surgery. Patients must have one of the following diagnostic codes:

Diagnostic Code
M16.0 Bilateral primary osteoarthritis of hip
M16.12 Unilateral primary osteoarthritis, Left hip
M16.11 Unilateral primary osteoarthritis, Right hip
M17.0 Bilateral primary osteoarthritis of Knee
M17.12 Unilateral primary osteoarthritis, Right knee
M17.11 Unilateral primary osteoarthritis, Right knee
M19.011 primary osteoarthritis, Right shoulder
M19.012 primary osteoarthritis, Left shoulder

In 2018, the orthopedic center conducted 355 primary knee, 283 primary hip, and 76 primary shoulder/reverse shoulder surgeries. Approximately 450 of these were completed by Drs. Marston and Myeroff, from whose patients we will be recruiting. We will also recruit from Drs. Reich, Pittman, and Huang.This excludes non-elective cases, revisions, removals, supplements, and unis. The goal of the study is to recruit n=100 subjects meeting inclusion and exclusion criteria (see below) undergoing elective hip, shoulder, or knee surgery.

i. *Inclusion Criteria*
    1. Age ≥50 and ≤90
    2. Any patient undergoing elective orthopedic surgery for hip, knee, or shoulder replacement (as defined by the codes above)

ii. *Exclusion Criteria*
    1. History of cognitive impairment of dementia
    2. MOCA <26
    3. History of Parkinson's disease, progressive supranuclear palsy, corticobasal degeneration, normal pressure hydrocephalus, Huntington's disease, stroke, seizure disorder, brain tumor, or brain surgery
    4. History of surgery requiring anesthesia within the past 3 months
    5. Non-English speaking

c. Data collection process

1. *Review of Schedules:* Prior to clinic visits, the orthopedic research assistant will review clinic schedules to identify potential subjects for the next day. Patients presenting for initial visit before elective orthopedic surgery for hip, knee, or shoulder replacement will be pre-screened for this study by orthopedic research assistant based on inclusion/exclusion criteria thorough review of the electronic medical record.
2. *Pre-Surgical Clinic Visits:* During the clinic visit, potentially eligible patients will be given a flyer describing the research study and asked if they are interested in participating. Any questions they have will be addressed. If they are interested, a screening visit will be scheduled and the patient will be given a copy of the informed consent to review at home. If the patient is unsure about participating, they will be sent home with the information and the neuroscience research assistant will follow-up with a phone call in about 3-5 days. There is no phone script for this call. They will be asked if they have further considered participating in the study, any questions they have will be answered,

and an appointment will be scheduled if they are interested. It is not feasible with the orthopedic clinic workflow to complete the MoCA screening during the clinic visit.

3. *Screening & Baseline Research Visits:* Combined screening and baseline visits will be held at the Neuroscience Center (NSC) or remote, via telephone or video (WebEx). Patients will be consented. A research assistant will review the inclusion and exclusion criteria. Patient demographic factors will be entered into case report forms (CRF) and then into REDCap. The patient will undergo a MOCA evaluation to confirm score≥26 if in person, or >19 for the MOCA Blind if completed remote. Should patients not meet the study threshold for MOCA, they will be counseled regarding their score and available resources. Patients scoring normally on the MOCA will undergo a cognitive battery performed by NSC research assistant. Patients will undergo a blood draw for NfL at NSC regardless of an in person visit or remote. The blood will be sent to a Boston-based laboratory for processing. Results from cognitive battery and blood draw will be entered into REDCap. Patients who complete screening will receive a $5 gift card. Patients who complete both the screening and baseline visits will receive a $10 gift card.
4. *Post-Surgical Clinic Visits:* Patients will return to orthopedic clinic for 3 month post-operative visit. This is not a research visit.
5. *Follow-Up Research Visits:* A follow-up visit will be scheduled at NSC or remote for 3 months post-surgery (+/- 2weeks). The cognitive battery will be administered. If it is desired by the patient, this visit can be coordinated so that it is paired with the orthopedic follow-up appointment, which is close in location. Results from cognitive battery will be entered into RREDCap. Patients who complete the follow-up research visit will receive a $10 gift card.

d. Intervention, treatments

A cognitive battery will be performed at baseline and then at 3 months post-operatively. A lab for NfL will be drawn during the screening/baseline visit. This is an observational study. There are no treatment interventions for this study.

e. Outcomes/endpoint and other variable definitions, and instruments used

Presence of POCD as determined by neuropsychometric outcome data at baseline and 3 months will be used as the outcome for all three study aims. The neuropsychological tests indicated have strong test-retest reliability. A reduction of 1.5 SD in any neuropsychological test between baseline and 3 months will indicate presence of POCD.

Cognitive Domain	Subtopic	Neuropsychological Test
Global Cognition		MoCA (versions 1 and 2)
Attention	Simple	WAIS-IV Digit Span Forward
	Complex/working mem	WAIS-IV Digit Span Backward
	Complex/working mem	Trails B
Learning/Memory	Immediate	HVLT (versions 1 and 4)

	Delayed	HVLT (versions 1 and 4)
	Psychomotor Speed	Trails A
	Psychomotor Speed	WAIS-IV Digit Symbol Coding
Mood	Anxiety	GAD-7
	Depression	GDS-15

f. Statistical analysis plan

The study population will be described by demographics (e.g. sex, age, race, education status) and baseline health (e.g. vision or hearing impairment, medical history). The appropriate summary measures (mean and standard deviation for continuous variables and frequencies for categorical variables) will be reported. Missing data will be assessed and if a large proportion of data is missing (>10%), we will compare baseline characteristics between subjects to determine if this subpopulation is significantly different. Imputation methods will be considered if differences are found. All statistical analyses will be performed in SAS v9.4 and evaluated at the 0.05 significance level, unless otherwise indicated.

Primary Aim: estimate the incidence of post-operative cognitive dysfunction three months after orthopedic surgical intervention.

This will be defined as a 1.5 SD decline from in any one of the cognitive domains tested baseline to three months. The proportion of patients who develop POCD and a 95% confidence interval will be reported.

Secondary Aim 1: determine pre and peri-operative risk factors associated with development of POCD.

We will be primarily interested in the association between incidences of POCD with the following risk factors:

1. History of delirium
2. Presence of post-operative delirium
3. Regional versus general anesthesia
4. >3 sedating medications added during hospitalization
5. History of prior surgery with general anesthesia

We will fit a logistic regression model with presence of POCD as the outcome of interest and the above risk factors as predictors of interest. We will also include age and gender. As an exploratory analysis, we will fit a model with additional risk factors and use score selection to keep variables with the most impact.

Secondary Aim 2: explore the role of serum neurofiliament light (NfL) in predicting risk for development of POCD.

A logistic regression model will be fit with presence of POCD as the outcome of interest and NfL as the predictor of interest to assess the predictive ability of NfL in the development of POCD. We will fit another logistic model that includes NfL and adjusts for the risk factors called out in Secondary Aim 1.

g. Power analysis or statement of precision

In 2018, the orthopaedic center conducted 355 primary knee, 283 primary hip, and 76 primary shoulder/reverse shoulder surgeries. Approximately 450 of these were completed by Drs. Marston and Myeroff, from whose patient populations we will be recruiting. This excludes non-elective cases, revisions, removals, supplements, and unis. The goal of the study is to recruit n=100 subjects. This n was based on both the number of patients we expect to be able to recruit during our timeline, and the estimated study budget. We anticipate the POCD incidence rate will be between 18 and 25% based on previous literature (Moller T et al Lancet 1998). A sample size of 100 produces a two-sided 95% confidence interval with a width equal to 0.157 when the sample proportion is 0.2. This calculation was done using the confidence intervals for one proportion procedure of PASS 2016.

h. Strengths and limitations

Strengths of this study include its focus on post-operative cognitive dysfunction, a topic that is not widely covered in the neurology, orthopedic or anesthesia literature. Furthermore, this study represents a more robust improvement over past investigations of post-operative cognitive dysfunction in normal aging adults in that the Montreal Cognitive Assessment (MOCA) rather than the Mini Mental Status Exam (MMSE) is being used to confirm normal cognition. The MOCA has a 90% sensitivity for mild cognitive impairment whereas the MMSE has an 18% sensitivity for mild cognitive impairment. This will be one of the first studies to evaluate patients exclusively undergoing elective orthopedic surgery whereas prior studies have looked at POCD following a combination of surgical procedures. Finally, this study can be considered pioneering in that it is the first to evaluate the association of blood NfL with risk of post-operative cognitive dysfunction.

Study limitations include the absence of immediate post-operative assessment that may be indicative of a delirium. Our budget allows for a cognitive assessment at baseline and then 3 months in n=100 subjects. We do not have the funding or infrastructure to evaluate patients within their first 3-7 days following surgery. Such information may be helpful in gauging risk for POCD. In addition, we would ideally like to be able to follow cognitive evaluations for 6 and 12 months post-operatively, but likewise do not have funding to evaluate cognition for this period of time while maintaining sufficient numbers of study subjects. Finally, we are unable to include imaging biomarkers of neurodegeneration such as hippocampal atrophy on brain MRI or FDG-hypometabolism of the precuneus/posterior cingulate as we do not have funding to support these diagnostic tests.

5. *Setting/Environment/Organizational feasibility*

The study will be conducted at both the HealthPartners orthopedics clinic as well as the Neuroscience Center. The orthopedics department performs 8-10 total joint surgeries per week with majority of procedures occurring in a population that is older than 50. Potential patients meeting the inclusion and exclusion criteria will be pre-screened at the orthopedics center. The HealthPartners Neuroscience Center has extensive experience with conducting clinical trials and administering neuropsychometric studies. At NSC, patients will undergo cognitive screening and neuropsychometric testing.

Dr. Rosenbloom is the HealthPartners Neurology Department and Clinical Director of the Center for Memory and Aging; he is serving as the principal investigator of this study. Dr. Switzer has obtained support from Dr Sarah Anderson, chair of orthopedics and has engaged two orthopedic clinicians, Drs Scott Marston and Chad Myeroff, to include his patients in this investigation.

A common concern expressed by aging patients encountered in both orthopedics and neurology is whether or not undergoing surgery with anesthesia will result in post-operative cognitive decline. Neurology has a department goal of facilitating healthy cognitive aging in the Twin Cities population and limiting environmental exposures that could potentially hasten progression to dementia. Furthermore, the HealthPartners orthopedics department is committed to reducing the risk of post-operative complications, including delirium and progressive cognitive impairment.

6. *Risks and Benefits*

Risks associated with the study include uncovering evidence of undetected cognitive impairment, which may be upsetting to the patient and family. At the same time, this information will be helpful in optimizing patient outcomes. Furthermore, patients will undergo a blood test for NfL that may result in brief discomfort.

Benefits of participating include the opportunity to obtain baseline cognitive testing results, which may better inform patients of current cognitive health. Furthermore, those patients who do end up performing abnormally on the MOCA will be referred for additional diagnostic work-up for dementia.

7. *Data Confidentiality and Privacy*

Data will be stored on a secured server with restricted access to the project folder. Participants will be identified by a study identification number. Secure surveys will be conducted through RedCAP. Data from the CRFs and the cognitive assessment score sheets will be entered into a secure RedCap database. A participant tracking database will also be created in RedCap. Neuroscience research study staff are experienced at building RedCap applications and using them for data entry and participant tracking.

8. *Timeline*

August 2019	Development of cognitive battery workflow
September 2019	Training of research staff in cognitive battery/submission to IRB
October 2019	Education of orthopedic providers re: cognitive assessment
November 2019	Initiate recruitment process
Nov 2019 – Feb 2021	Administration of cognitive battery at baseline and 3 months
March 2021	Data analysis

April 2021	Manuscript preparation/discuss at neurology & orthopedic meetings throughout organization
May 2021	Evaluate inclusion of cognitive battery as a standard clinical initiative in orthopedics
July 2021	Presentation at AAIC Conference
March 2022	AAOS Conference
June 2022	AOA Conference

9. Dissemination/Sharing Results/Integration and Impact

Results from this investigation will be shared during department meetings for neurology and orthopedic surgery, respectively. Furthermore, a presentation will be performed for the Regions HLT meeting as this was a Red-funded grant. Efforts will be made to discuss findings with Park Nicollet neurology and orthopedic departments if it is determined from this study that certain pre-surgical factors are predictive of post-operative cognitive dysfunction.

For external communication, Dr. Rosenbloom and his team attend annual neurology meetings that include the American Academy of Neurology as well as the Alzheimer's Association International Conference. Dr. Switzer and colleagues attend annual orthopaedic meetings that include the American Academy of Orthopaedic Surgeons as well as the American Orthopaedic Association. There are plans to submit these results for a poster/oral session at each of these meetings.

Finally, our plan is to eventually submit a manuscript documenting our findings relating demographic risk factors and NfL levels to post-operative cognitive dysfunction. Hopefully, this publication will support our application for a larger, NIH grant for the study of a larger cohort of surgical patients and potential interventions for post-operative cognitive dysfunction.

10. References

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