COVER PAGE

Official Title of Study: Time to Post-Anesthesia Neurological Evaluation With Three Different Anesthetic Techniques

Clinicaltrials.gov number: NCT03996148

Date of Document: April 3rd, 2019

Investigator-Initiated Protocol Template

Title Of Project: Postoperative Neurological Function And Hemodynamic Stability In Carotid Endarterectomy Comparing Three General Anesthetic Techniques: A Pilot Study.

Principal Investigator and Department:
Rhea Temmermand, CRNA, MSN; Anesthesiology

Co-investigators and Departments/Institution:

Dejan Vuckovic, MD; Anesthesiology
Jonathan Rost, MD; Anesthesiology
Ludmil Mitrev, MD; Anesthesiology
Frank Caputo, MD; Vascular Surgery
Dean Roberts, CRNA, MSN; Anesthesiology
John Gaughan, PhD; Biostatistics

A Objectives/Purpose

The objective of this pilot study is to analyze the differences in time to first postoperative neurological response (cranial nerve XII – tongue movement, movement of extremities) and in hemodynamic stability when three different general anesthetic techniques are used for carotid endarterectomy. Patients who emerge from general anesthesia, follow commands, and meet extubation criteria sooner reassure the surgical team they have returned to their baseline neurological status. Failure to return to baseline neurologic status may require early intervention through surgical re-exploration or CT scan.

B Hypotheses

Our hypothesis is that there is a clinical and statistically-significant difference in time to first post-operative neurologic response between subjects undergoing carotid endarterectomy with three anesthetic techniques where the depth of anesthesia is titrated to a bispectral index (BIS) of 50-60.

C Background

Carotid endarterectomy reduces the incidence of stroke in people with symptomatic, severe carotid artery stenosis. However, there are risks associated with this procedure such as stroke from carotid clamping with poor collateral brain circulation or embolization of carotid plaque debris (Sheth, 2017). Few surgeons monitor the brain during the procedure using SSEP or EEG, as most rely on intraoperative blood pressure management, shunting, and postoperative neurological exam (De Santis, 2016; Kobayashi, 2011).

A Cochrane review of regional versus general anesthesia for carotid endarterectomy reveals no significant difference in outcomes (Vaniyaping, 2013). It is common practice at Cooper Hospital to deliver general anesthesia. The general anesthetic given may affect the length of time to first post-operative neurological response and the hemodynamic stability, though this is not well studied.

A search in PubMed in April 2017 for “carotid endarterectomy AND (general anesthesia OR total intravenous anesthesia OR regional anesthesia) AND neurologic exam” ("endarterectomy, carotid"[MeSH Terms] OR ("endarterectomy"[All Fields] AND "carotid"[All Fields]) OR "carotid endarterectomy"[All Fields] OR ("carotid"[All Fields] AND "endarterectomy"[All Fields])) AND (("general anaesthesia"[All Fields] OR "anesthesia, general"[MeSH Terms] OR ("anesthesia"[All Fields] AND "general"[All Fields]) OR "general anesthesia"[All Fields] OR ("general"[All Fields] AND "anesthesia"[All Fields])) OR (total[All Fields] AND ("intravenous anaesthesia"[All Fields] OR "anesthesia, intravenous"[MeSH Terms] OR ("anesthesia"[All Fields] AND "intravenous"[All Fields]) OR "intravenous anesthesia"[All Fields] OR ("intravenous"[All Fields] AND "anesthesia"[All Fields])))) OR ("regional anaesthesia"[All Fields] OR "anesthesia, conduction"[MeSH Terms] OR ("anesthesia"[All Fields] AND "conduction"[All Fields]) OR "conduction anesthesia"[All Fields] OR ("regional"[All Fields] AND "anesthesia"[All Fields]) OR "regional anesthesia"[All Fields])) AND (neurologic[All Fields] AND exam[All Fields]) revealed no studies comparing anesthetic types and time to first post-operative neurological response in this surgical population. Through anecdotal experience at Cooper Hospital, patients are noted to emerge faster and follow commands sooner when not given preoperative midazolam and given a combined Total Intravenous Anesthetic (TIVA) and volatile inhalational anesthetic technique titrated to a bispectral index (BIS) of 50-60.

D Significance of the research

Ruling out anesthetic causes of abnormal neurological function is vital in this patient population. Neurological dysfunction that is surgical in nature may require early intervention such as surgical reexploration or CT scan. “Time is brain”, and a few minutes difference is enough to cause permanent neurological damage if a progressing stroke is not quickly identified. Anesthetic techniques that demonstrate a quicker return to baseline neurological function will greatly benefit this surgical patient population.

E Study Design

This is a prospective, randomized, single-blind (patient only) pilot study. Patients coming to Cooper Hospital to have a carotid endarterectomy and are enrolled in this study will be randomized into one of three groups. No group will be administered midazolam or other benzodiazepines. Study group A will receive a maintenance anesthetic consisting of propofol, remifentanil, and 0.5 minimum alveolar concentration (MAC) desflurane. Study group B will receive a maintenance anesthetic consisting of dexmedetomidine, remifentanil, and 0.5 MAC of desflurane. Study group C will receive a maintenance anesthetic consisting of only propofol and remifentanil. The control group will receive only remifentanil and desflurane for maintenance of anesthesia.

In all three groups, the depth of anesthesia will be titrated to a BIS of 50 to 60. The titration in group A and B will occur by first varying the propofol or dexmedetomidine infusion dose while maintaining the dose of desflurane at 0.5 MAC for as long as possible. Only if it proves difficult to maintain the BIS between 50-60, and after adjustment of the intravenous anesthetic, will the anesthesiologist, at his or her discretion, titrate the dose of desflurane up or down as needed to maintain BIS in the prescribed range.

Induction will be achieved by using propofol or etomidate, with or without fentanyl, in the usual doses. Lidocaine 100mg IV will be used in all subjects to pretreat the patient's vein and avoid the pain of propofol injection. Fentanyl or any other narcotic with the exception of remifentanil will not be re-administered until after the first post-operative neurological exam. The surgeon will be asked to infiltrate the surgical field (incision, area around the carotid bulb) with 1-2% lidocaine and/or 0.25% bupivacaine for achievement of local analgesia.

Rocuronium, vecuronium or cisatracurium will be used for muscle relaxation. Other agents with known hypnotic or psychotropic effects, such as, for example, diphenhydramine, will be avoided and only used if required as rescue medications. All other required drugs will be used in standard-of care doses in all 3 groups (reversal agents, vasoactive or cardiac drugs) and titrated at the discretion of the anesthesia provider. No group will receive ketamine.

All subjects shall have an arterial line placed for blood pressure monitoring and titration of vasoactive agents. This is standard of care and not for purposes of the study.

F Research Plan

IRB-approved informed consent will be obtained from subjects presenting for carotid endarterectomy. Study consent will be obtained by the investigators in person no later than the morning of surgery. Patients will then be randomized consecutively to one of the three treatment groups using a randomized allocation schedule. The anesthesia provider (co-investigators) for the case will be informed of the anesthetic group and will deliver anesthesia per study protocol.

1 Subjects

a Number of Subjects: there is insufficient historical data in the literature to estimate potential differences in the time until an adequate neurological response among the treatment groups. For this reason we plan to include up to 10 patients in each group to determine differences that can be used for planning a larger definitive study with appropriate power.

b Exclusion and Inclusion criteria

Inclusion: patients receiving carotid endarterectomy, at least 18 years old, must be able to give consent, must be able to undergo a preoperative neurological exam.

Exclusion: pregnant patient; prisoners; dementia or reduced mental status for any reason, acute or chronic; known brain tumor or head trauma; known severe CAD (uncorrected); EF < 15%; IABP or other mechanical circulatory assist device; severe COPD; uncontrolled/severe anxiety requiring benzodiazepine administration; history of difficult airway; sedation other than propofol, dexmedetomidine or volatile anesthetic agent (VAA) is needed for patient (i.e. ketamine in patients with a history of neuropathic pain); intubated or unconscious patients; patients on methadone or fentanyl patch; known unusual or extreme anesthetic requirements, unusual amount of narcotic needed to control pain; surgeon requests local-regional anesthesia only (not general anesthesia); known history of prolonged emergence; morbidly obese patients (BMI > 40); inability to apply BIS monitor strip (scalp or forehead defects).

c Recruitment Methods: Subjects will be recruited through the OR schedule. A co-investigator may speak with the patient via phone before the surgery to describe the study and obtain study consent in person the morning of surgery. The patients will usually be same-day admits, but inpatients are not excluded from consideration.

d Informed Consent Process: All prospective subjects will be approached concerning participation in this study by a co-investigator from the Department of Anesthesiology no later than the morning of surgery.

e Vulnerable Subjects: excluded per the exclusion criteria

f Compensation to Subjects: No compensation

g Treatment for Research-Related Injuries: Research related injuries are not anticipated but will be dealt with using standard procedures at Cooper University Hospital. The expenses will be billed to the subjects' insurance provider.

2 Research Methods and Procedures

After receiving informed consent, subjects will be randomized into one of 3 groups:

Study group A: no midazolam given; maintenance drugs started immediately after induction and airway is secured.
Remifentanil - titratable; initial starting dose 0.05 mcg/kg/min
Propofol – titratable; initial starting dose 75 mcg/kg/min
Desflurane 0.5 MAC

Study group B: no midazolam given; maintenance drugs started immediately after induction and airway is secured.
Remifentanil - titratable; initial starting dose 0.05 mcg/kg/min
Dexmedetomidine – titratable; initial starting dose 0.5 mcg/kg/hr
Desflurane 0.5 MAC

Study group C: no midazolam given; maintenance drugs started immediately after induction and airway is secured.
Remifentanil - titratable; initial starting dose 0.05 mcg/kg/min
Desflurane – titratable

Postoperative: Anesthesia providers will note the "surgical end" time which is when the surgical site is closed and the final sterile dressings are placed. Upon emergence, CN XII and gross motor neurological exam will be performed every minute (or less) until extubation, or every 3 minutes (or less) in the PACU until a normal neurological response is achieved or a decision is made for some form of further intervention (observation, CT scan, or surgical re-exploration). The time to the first adequate neurologic response will be noted and will be the main outcome variable.

Surgical fellows/residents and attendings, anesthesia providers and PACU nurses who have been trained in the neurological exam may administer it and note the time.

Study participation will end when the subject is discharged from the hospital or 48 hours post-op, whichever occurs first. Patients will be followed during this time by bedside visit and/or EPIC chart review. Any postoperative complications during the first 48 hours or until discharge will be noted. Length of PACU and hospital stay will be recorded.

3 Data Analysis Plan, Statistical Tests, and Sample Size Rationale

In order to carry out a pilot study of the alternative anesthesia options, up to 10 subjects per group (3 groups) will be included in the study to determine differences that can be used for planning a larger definitive study with appropriate power.

Variables to be collected:

- Age
- Gender
- Height

- Weight
- Preoperative and postoperative responses to neurological exam (intact vs. deficits)
- 3-minute Confusion Assessment Method (3D-CAM) and Short Blessed Test (SBT). The former will be re-administered daily until the second postoperative day or discharge, whichever occurs first. The SBT will be re-administered 1 week postoperatively via telephone interview.
- Postoperatively will collect time from 'surgery end' until following any command, sticking out tongue, squeezing both hands, moving both feet
- Preoperative, intraoperative and postoperative hemodynamic measures: blood pressure, heart rate
- Intraoperative use of cardiac drugs: vasopressors, vasodilators, beta blockers, calcium channel blockers or any other drugs used to control blood pressure and heart rate – total dose
- Intraoperative arterial blood pressure at intervals no less than every 5 minutes
- Intraoperative fluid administration (total)
- Intraoperative blood loss (EBL)
- Carotid clamp time
- Use of carotid shunt (yes/no)
- Use of SSEPs requested by surgeon (yes/no)
- Surgery end time to extubation time
- Surgery end time to first adequate neurologic response: MAIN OUTCOME VARIABLE
- BIS throughout the intraoperative portion of the case no less than at 15 minute intervals
- Hospital length of stay
- PACU length of stay in hours
- Post-operative complications experienced by subject (e.g. stroke, seizure, MI, sepsis, prolonged hospitalization >48 hours, respiratory failure requiring prolonged mechanical ventilator support, prolonged awakening from anesthesia (>30 min), pneumonia, DVT, PE, post-operative nausea and vomiting)

Statistical analysis

Categorical data will be summarized as N (%), continuous variables as mean ± standard deviation (SD) or median ± interquartile range (IQR), depending on the distribution of the data. Normality of the data will be assessed using the Kolmogorov-Smirnov test. Categorical data will be compared using chi-squared tests and continuous variables using ANOVA. Post-hoc testing using Holm-Sidak tests or Dunn's tests will be performed if a difference exists among the 3 groups to assess pairwise differences. A p-value of < 0.05 will be considered statistically significant.

Since no effect size data exists in prior literature, no power calculation will be done. We estimate that 5-6 subjects per group will be sufficient to get an impression of differences to first neurological exam, since the aim of the study was to facilitate potential larger subsequent trials.

G Risks and Benefits

1 Potential Risks to Subjects and How They Will Be Minimized

All of the described anesthetic methods in the three study groups are commonly used in

practice and can be considered standard of care. Participation in this study therefore does not add any study-related risk to patients. These drugs are currently being used to deliver general anesthesia to patients for this procedure. This is not an off-label use of these drugs and these drugs are being given at acceptable dosages for general anesthesia. If for some unexpected and unforeseen reason the patient does not appear to tolerate the prescribed anesthetic regimen, the anesthesiologist will be allowed to modify the regimen as needed to keep the patient safe. The intention to treat principle will be used in the subsequent analysis.

2 Potential Benefits

Patients may theoretically emerge faster and follow commands sooner in the study groups, but in the absence of prior data, this is unknown. Ruling out anesthetic causes of delayed normal neurological function may alert the surgical team sooner if there is a possibility of a stroke. Faster recognition of a stroke will allow the surgical team to place the patient back under anesthesia for surgical re-exploration or send the patient to CT scan sooner. This unique surgical population can benefit neurologically from a few minutes difference in recognition time. Furthermore, this study will assess the general anesthetic type and the hemodynamic stability during CEA.

3 Risk:Benefit Ratio

The aforementioned potential benefits outweigh the potential risks. There are no potential risks specific to the study procedures that are different from, or exceed, the risk of the surgery and the anesthesia, which are well-known and not related to the study procedures.

H Plans for Monitoring Subject Safety

Patients will undergo standard monitoring for general anesthesia which includes certified anesthesia providers, preoperative and postoperative nurses, and other trained surgical staff (surgical attending, fellow and resident) during the perioperative period. Standard monitors will be applied including EKG, blood pressure (arterial line and NIBP), pulse oximetry, end-tidal CO2 monitoring and BIS monitoring. Any additional drugs or treatments not mentioned in this protocol but required to care for the patient will be given without restriction at the discretion of the anesthesiologist and surgeon.

I Procedures to Maintain Privacy and Confidentiality

Co-investigators will only use subject numbers on data sheets. Identifying data will be

kept in a study patient shortlist in EPIC and a separate password-protected, encrypted Excel file maintained on the anesthesia drive on the Cooper network. The study folder with original consent forms and regulatory documents will be kept in a locked cabinet on 4 Dorrance in the anesthesia research office.

J References

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