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Rationale and design for the detection and neurological impact of cerebrovascular events in non-cardiac surgery patients cohort evaluation (NeuroVISION) study: a prospective international cohort study

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ABSTRACT

Objectives Covert stroke after non-cardiac surgery may have substantial impact on duration and quality of life. In non-surgical patients, covert stroke is more common than overt stroke and is associated with an increased risk of cognitive decline and dementia. Little is known about covert stroke after non-cardiac surgery. NeuroVISION is a multicentre, international, prospective cohort study that will characterise the association between perioperative acute covert stroke and postoperative cognitive function.

Setting and participants We are recruiting study participants from 12 tertiary care hospitals in 10 countries on 5 continents.

Participants We are enrolling patients ≥65 years of age, requiring hospital admission after non-cardiac surgery, who have an anticipated length of hospital stay of at least 2 days after elective non-cardiac surgery that occurs under general or neuraxial anaesthesia.

Primary and secondary outcome measures Patients are recruited before elective non-cardiac surgery, and their cognitive function is measured using the Montreal Cognitive Assessment (MoCA) instrument. After surgery, a brain MRI study is performed between postoperative days 2 and 9 to determine the presence of acute brain infarction. One year after surgery, the MoCA is used to assess postoperative cognitive function. Physicians and patients are blinded to the MRI study results until after the last patient follow-up visit to reduce outcome ascertainment bias. We will undertake a multivariable logistic regression analysis in which the dependent variable is the change in cognitive function 1 year after surgery, and the independent variables are acute perioperative covert stroke as well as other clinical variables that are associated with cognitive dysfunction.

Conclusions The NeuroVISION study will characterise the epidemiology of covert stroke and its clinical consequences. This will be the largest and the most comprehensive study of perioperative stroke after non-cardiac surgery.

Trial registration number NCT01980511; Pre-results.

Strengths and limitations of this study

- ► A blinded study design in order to minimise bias in characterising the impact of postoperative covert stroke on cognitive function.
- ► A method of evidence-informed data imputation to minimise systematic bias from incomplete cognitive assessments.
- ► The Montreal Cognitive Assessment instrument used to measure cognitive function is clinically relevant and assesses multiple cognitive domains.
- ► Cognitive testing instruments may be insensitive to subtle changes in cognitive function.
- ► Availability of MRI scanners precluded the enrolment of all eligible patients.

INTRODUCTION

Worldwide, 200 million adults have non-cardiac surgery requiring hospital admission annually.[1] Non-cardiac surgery provides

substantial benefit to most patients; however, it is associated with major vascular complications including myocardial infarction, cardiac arrest, stroke and death. Although only a small proportion of patients will suffer a clinically overt perioperative stroke (~0.5%), these events often have a devastating effect on patients' quality and duration of life.[2] It is likely that there are many more covert than overt strokes, but the incidence of covert brain infarcts after non-cardiac surgery, and their implications for patients and families remain unknown.

Perioperative overt stroke

The true incidence of overt stroke after non-cardiac surgery remains unknown, and the estimates of the risk of stroke in the current literature vary from 0.2% to 4.3%.[3–5] Stroke and postoperative cognitive dysfunction are of the utmost concern to patients. A study of 1216 patients identified common fears when facing elective knee surgery, and found that the largest proportion of participants were 'very concerned' about perioperative 'brain damage' (19%, 234/1216), followed by 'memory loss' (17%, 210/1216).[6] In contrast, only 12% (147/1216) were very concerned about death in the perioperative period.

In the Perioperative Ischemic Evaluation (POISE) Trial (international randomised trial of 8351 patients from 190 centres in 23 countries),[2] stroke carried a high degree of morbidity and mortality. Among the 0.7% of patients who suffered a stroke, 32% died within 30 days and, of the survivors, 58% were left with major disability. In comparison, a meta-analysis of patient-level data from 1384 participants allocated to the placebo group of six major randomised controlled trials conducted outside of the perioperative setting demonstrated substantially lower mortality (13% died within 3 months) and morbidity (28% suffered a major disability). Moreover, these non-operative studies excluded patients with minor strokes.[7]

The high incidence of death and disability after perioperative stroke compared with stroke in the ambulatory setting suggest the possibility that we may be missing some strokes with mild or moderate severity after surgery, and these covert events may be prognostically important.

Perioperative covert brain infarction

Covert stroke is an acute ischaemic event that has no apparent clinical manifestations, but may increase the risk of cognitive and physical decline.[8 9] Modern neuroimaging techniques (MRI sequences) can detect acute covert stroke with a high degree of accuracy.[10] Several large studies have evaluated the prevalence of covert stroke in the general population of older adults, but only a few small studies have evaluated the frequency of covert stroke in the perioperative setting after cardiac and carotid artery surgery, but not after non-cardiac surgery.

No study has examined the association of covert stroke with cognitive decline after surgery. In the non-surgical population, evidence suggests covert stroke is associated with, and may be causally related to, dementia and cognitive decline,[11] as well as impairments in activities of daily living.[12]

OBJECTIVES OF THE NEUROVISION STUDY

The NeuroVISION study aims to characterise the incidence, impact and risk factors of covert stroke in adults undergoing non-cardiac surgery. We will do this using a postoperative MRI study of the brain completed 2–9 days after surgery and follow-up assessment of neurocognitive function.

Primary outcome

The primary outcome is postoperative cognitive dysfunction, defined as a decrease of two or more points on the Montreal Cognitive Assessment (MoCA) scale from preoperative baseline to 1-year follow-up. We hypothesise that perioperative covert stroke is associated with cognitive dysfunction 1 year after surgery. We believe that cognitive assessment at 1 year after surgery informs the long-term impact of covert stroke, while cognitive assessments performed sooner after surgery may be affected by postoperative changes (eg, incisional pain, analgesics and surgery-related functional limitations).

The National Institute of Neurological Disorders and Stroke (NINDS) has coined the term 'vascular cognitive impairment' (VCI) for neurological dysfunction that is caused by, or associated with vascular factors.[13] They have recommended the MoCA instrument as a tool for neurocognitive testing of patients with suspected VCI,[13] and MoCA has shown good correlation when compared with the full 60 min NINDS VCI Battery neuropsychological assessment.[14]

MoCA is used extensively in the assessment of cognitive function after stroke and cerebrovascular disease.[14–18] It is superior to the Mini-Mental State Examination (MMSE) in assessments of language skills, visual-spatial and executive function, and in the diagnosis of cognitive dysfunction after stroke.[15 17] MoCA assesses multiple cognitive domains, and it provides a thorough assessment of the impact of perioperative covert brain infarction. The MoCA instrument is more sensitive than the MMSE, and has a minimal ceiling effect.[19] We will exclude patients with a history of dementia, thereby minimising the risk of floor effect with respect to the change in cognitive score.

Cognitive decline due to the ageing process is associated with lower MoCA scores. Previous studies have shown a decline of 1.4 –2.2 points on the MoCA score for every additional 10 years of age in patients 65 years of age and older[20 21] It can be interpreted that a two-point difference in the MoCA score represents 10 years of brain ageing, and this would be relevant to patients and their caregivers. A change of two points on the MoCA score has been used as a cut-off for significant cognitive decline in published studies.[22]

METHODS

Study design

The NeuroVISION Study is a multicentre, prospective cohort study being conducted in 12 tertiary hospitals from 10 countries on 5 continents.

Study population

We are enrolling patients ≥65 years of age, requiring hospital admission after non-cardiac surgery, and have an anticipated length of hospital stay of at least 2 days after elective non-cardiac surgery that occurs under general or neuraxial anaesthesia. We obtain consent for participation in NeuroVISION from the patients before surgery.

Patients who have a contraindication to MRI scanning (eg, implanted devices not safe for MRI studies, claustrophobia), patients who are unable or unwilling to attend the follow-up appointments, patients who have a documented history of dementia as diagnosed by a physician or who reside in a nursing home, and patients undergoing carotid artery surgery or intracranial surgery are excluded from the study. We are also excluding patients who are not able to complete neurocognitive testing due to language, vision or hearing impairment, those who are not able to communicate with the research staff due to language barriers, patients who do not consent to participate, and those who were previously enrolled in the NeuroVISION Study.

Patient and public involvement

Patients and public were not involved in the development of the research question or the design of the study. Study results will be disseminated by publication in a medical journal, and poster presentation at a medical conference.

Sampling strategy

In the NeuroVISION Pilot Study,[23] there were approximately 15–30 eligible patients per centre each week, but due to limitations on the availability of the MRI scanners, each centre could only recruit up to two patients per week. Because of the disparity between the number of eligible patients and the MRI capacity, we are employing a sampling strategy to ensure proportionate representation of patients that reflects the overall surgical population by randomly assigning the days of recruitment for specific surgery subtypes, proportional to the prevalence of surgery type at each local centre.

Clinical data collection

Research personnel approach all patients who fulfil the eligibility criteria to obtain informed consent before the day of surgery. After obtaining written informed consent from eligible patients or their legal decision-makers, research personnel administer the MoCA questionnaire, the Digit-Symbol Substitution Test (DSST)[24] and the Trail-Making Test Part B (TMT-B)[25] to assess baseline cognitive function. They also administer the Lawton Instrumental Activities of Daily Living (iADL) Scale,[26] modified Rankin Scale,[27] Geriatric Depression Scale (GDS)[28] and the EQ-5D questionnaire[29] to assess physical function, mood and health-related quality of life at baseline. The research personnel interview patients and review their charts to obtain baseline clinical information including patient demographics (age, sex and ethnicity), medical history (eg, prior cerebrovascular disease, other vascular risk factors and adverse cardiac events, venous thromboembolic disease, depression and anxiety, and respiratory diseases) and medication use prior to surgery (eg, cardiac medications, antiplatelet agents and anticoagulants, narcotics and other psychoactive medications).

Research personnel follow patients until hospital discharge. The patients are screened for delirium two times per day during the first 72 hours after surgery. Assessment for delirium is performed using the confusion assessment method.[30] Study personnel also collect detailed haemodynamic data as well as predefined clinical outcomes (overt stroke or transient ischaemic attack (TIA), adverse vascular events, bleeding, infection and kidney injury) occurring during the hospital stay.

Research personnel contact patients by phone 30 days after surgery. They collect data regarding predefined clinical outcomes (overt stroke or TIA, adverse vascular events, bleeding, infection and kidney injury), and administer the Lawton iADL Scale, Modified Rankin Scale, GDS and EQ-5D questionnaires. At 1 year after surgery, research personnel assess the patients in person. They collect data regarding predefined clinical outcomes (overt stroke or TIA, adverse vascular events, incident dementia, incident depression or anxiety), and administer the MoCA, DSST, TMT, Lawton iADL Scale, Modified Rankin Scale, GDS and EQ-5D questionnaires.

Detection of acute stroke in the perioperative setting

Acute postoperative covert stroke is detected using an MRI study of the brain performed between postoperative days 2 and 9, as early as the patient can tolerate the procedure. The majority of the covert strokes occurred by postoperative day 2 in previous large perioperative trials,[2 31] and we have chosen the timing of MRI on the basis of this experience, as well as the similarity to prior protocols.[32–34]

The MRI sequences consist of axial fluid-attenuated inversion recover (FLAIR), gradient echo (GRE), T2 and diffusion-weighted imaging (DWI) with apparent diffusion coefficient (ADC) mapping. MRI sequences are performed according to the local standard of care with a minimum 1.5 T MRI machine, and a slice thickness of 3–5 mm, with no gap. The DWI sequence has the ability to detect acute cerebral ischaemia that has occurred during the time window of minutes before the study up to approximately 10 days prior.[35] Therefore, it is not necessary to obtain a preoperative MRI scan in order to detect new covert brain infarctions. DWI MRI is very sensitive for the diagnosis of cerebral ischaemia, approaching 100%.[10 35] Where relevant, we use the ADC maps to aid us in determining whether a DWI lesion is new or old: a component of the DWI signal comes from T2 prolongation, and discriminating new from chronic lesions is

routinely done by assessing the ADC map for evidence of restricted diffusion.

Patient identifiers are removed, and MRI images are electronically transferred via a secure encrypted connection to the central imaging core laboratory. Two separate teams of clinicians with expertise in neuroradiology independently assess the studies in duplicate and provide a consensus interpretation regarding the presence of imaging lesions that represent acute perioperative cerebral ischaemia and chronic ischaemic findings, haemorrhages and white matter hyperintensities, defined according to consensus criteria.[36] Any disagreements are resolved by consensus. These clinicians are blinded to the baseline characteristics and clinical outcomes.

Ethics and blinding of the MRI study results

The results of the MRI scans are blinded until after the last patient follow-up visit. However, the MRI scans are reviewed immediately after image acquisition for clinically relevant non-ischaemic incidental findings. If identified, these findings are immediately reported to the study team and the attending physician involved in the care of the patient, and recorded in the study database. This protocol is in keeping with the Canadian Tri-Council policy defined in 'Ethical Conduct for Research Involving Humans',[37] as well as previously published literature.[38] The research ethics board at each site approved the protocol prior to patient recruitment.

We blind healthcare providers and patients to the MRI results for the following reasons: (1) blinding of study results eliminates potential bias in the ascertainment of study outcomes; (2) this study is not a part of the standard of care in the postoperative period; (3) the implications of acute covert stroke in the perioperative period are unknown and any management decisions on the basis of the MRI study would not be based on evidence but could positively or negatively impact outcomes; (4) any incidental finding, such as a tumour, is communicated to the attending physicians, as soon as the scan is read and (5) the research MRI study will be available for future comparisons if required for clinical care after the completion of the study.

Sample size

Our sample size calculation was based on our primary objective, the proportion of patients with a decrease of two or more points on the MoCA scale from preoperative baseline to 1-year follow-up. We will undertake a multivariable analysis to determine if postoperative covert stroke is associated with the incidence of postoperative cognitive dysfunction as measured by the MoCA, at 1 year after surgery (ie, the dependent variable). The International Study of Postoperative Cognitive Dysfunction 1 of postoperative cognitive dysfunction in patients aged 60 years or older[39] demonstrated a 9.9% incidence of postoperative cognitive dysfunction 3 months after surgery (95% CI 8.1% to 12.0%), while a subsequent study[40] showed an incidence of 12.7% in patients over the age of 60 (95% CI 8.9% to 16.4%). Increasing age was associated with an increased risk of cognitive dysfunction (5.7% in patients under 60 vs 12.7% in patients 60 years or older, p<0.001). Our study recruits patients who are at least 65 years old, and the risk of cognitive dysfunction may be even greater in this group. From non-operative literature, we expect that covert stroke will be associated with at least a twofold increase in the risk of cognitive dysfunction.[11 41]

A sample size of 900 patients would allow us to detect a minimum OR of 1.89 for the risk of cognitive dysfunction after a covert perioperative stroke, with 80% power and a two-sided alpha of 0.05, assuming a 30% incidence of postoperative cognitive dysfunction and a 10% incidence of postoperative covert brain infarction. A sample size of 1000 patients would allow us to detect a minimum OR of 1.93 for the risk of cognitive dysfunction after a covert perioperative stroke, with 80% power and a two-sided alpha of 0.05, assuming a 20% incidence of postoperative cognitive dysfunction and a 10% incidence of postoperative covert brain infarction. A sample size of 1100 patients would allow us to detect a minimum OR of 2.17 assuming a 10% incidence of postoperative cognitive dysfunction and a 10% incidence of covert stroke, and would allow us to detect a minimum OR of 2.18 assuming a 30% incidence of postoperative cognitive dysfunction and a 5% incidence of covert stroke (see table 1).

Analysis plan for primary objective

Our primary objective is to characterise the impact of postoperative covert stroke on neurocognitive function 1 year after elective non-cardiac surgery. We will undertake a multivariable logistic regression analysis to develop a model in which the dependent variable is a decrease in the MoCA score of ≥2, 1 year after surgery compared with the baseline measurement. The independent variables

Table 1 Minimum detectable ORs at a power of 80% and alpha of 0.05 for a given sample size, according to incidence of cognitive dysfunction and covert stroke

Incidence of covert stroke	Incidence of postoperative cognitive dysfunction								
	10%			20%			30%		
	Sample size (no of patients)			Sample size (no of patients)			Sample size (no of patients)		
	900	1000	1100	900	1000	1100	900	1000	1100
5%	2.96	2.83	2.72	2.49	2.39	2.31	2.36	2.26	2.18
10%	2.32	2.24	2.17	1.99	1.93	1.88	1.89	1.83	1.78

Table 2 Evidence-informed data imputation of missing data for cognitive assessments

Probability of cognitive decline	Reported reasons for missing	Data imputation	Missing data classification
Confirmed	New diagnosis of dementia	Multiple imputations centred at the average MoCA score change for patients with new diagnosis of dementia, mild cognitive impairment or those started on medication to treat cognitive impairment.	Informative missing
	New diagnosis of mild cognitive impairment		
	Started a medication to treat cognitive impairment (acetyl cholinesterase inhibitor, NMDA-receptor antagonist)		
Probable	New diagnosis of stroke	Multiple imputations centred at the average MoCA score change for those with MRI finding of old stroke or old cerebral small vessel disease	
	Cardiovascular death		
	Impairment on other related scale: decreased iADL (Lawton), depression (GDS)		
	Admission to long-term care facility or similar institution		
	Significant cognitive impairment reported by family or caregiver		
Unlikely	Refusal or missed, but reported well	Multiple imputations centred at zero change in MoCA value	
Unknown	Lost to follow-up (likely <1%)	Imputed directly through mixed model	Missing at random

GDS, Geriatric Depression Scale; iADL, Lawton Instrumental Activities of Daily Living; MoCA, Montreal Cognitive Assessment; NMDA, N-methyl-D-aspartate.

are acute covert stroke in the perioperative setting (we will exclude patients who suffer an acute clinically symptomatic stroke in the time period between surgery and the MRI study, but expect this event to be very infrequent); history of stroke, coronary artery disease or peripheral vascular disease; depression; age; sex; baseline neurocognitive function as measured by MoCA; baseline physical impairment as measured by the Lawton scale; discontinuation of opioid or benzodiazepine medication; initiation of cholinesterase inhibitor and surgery type.

For all regression models, we will report the ORs, 95% CIs and associated p values. For all tests, we will use a two-sided alpha <0.05 level of significance. Examination of residuals will provide an assessment of model assumptions for regression analyses. Goodness of fit for the models will be assessed using appropriate Hosmer-Lemeshow tests. For multivariable regression analysis, we will assess for multicollinearity (correlations among predictor variables)[42] using the variance inflation factor (VIF), which measures the extent to which the variance of the model coefficients is inflated (because of the correlation of the variable with other predictor variables) if that variable is included in the model. We will consider variables with VIF >10 collinear, and if this occurs, we will exclude one of the collinear variables from the analysis.

Approach to missing data

Even small proportions of missing data can bias study results, and cognitive decline may increase the risk of loss to follow-up and the risk of incomplete cognitive assessment. This may introduce systematic bias in the study analysis. It is possible to counteract this bias if the reason for missing data is known.[43 44] We are collecting the reasons for missing data, and will use a method of evidence-informed data imputation to minimise systematic bias from incomplete cognitive assessments (see table 2).

CONCLUSION

Non-cardiac surgery is common, but despite evidence that perioperative brain damage and cognitive dysfunction is a major concern to patients undergoing elective surgery, there are limited data regarding the epidemiology of cerebral ischaemia during this period. If the non-cardiac surgery setting is similar to the non-operative and cardiac surgery evidence regarding covert stroke, upwards of 10 million adults worldwide may suffer perioperative covert brain infarctions. The NeuroVISION study will characterise the epidemiology of covert stroke and its clinical consequences. This is the largest study of perioperative covert stroke after non-cardiac surgery and will provide important insights for the millions of elderly adults undergoing non-cardiac surgery annually.

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