PCRC Project Proposal Cover Sheet

Title: The Role of B Blockers in Stroke after Noncardiac Surgery: An Observational Study from the Multicenter Perioperative Outcomes Group

Principal Investigator: Phillip E. Vlisides, M.D.

Senior Investigator/Mentors: George A. Mashour, M.D., Ph.D., Sachin Kheterpal, M.D., M.B.A.

Study Type: Retrospective, observational cohort study

Primary Hypothesis: Incidence of perioperative stroke in noncardiac surgery patients taking β blockers varies inversely with selectivity for the β-1 adrenergic receptor.

Secondary Objectives: Assess granular clinical characteristics of postoperative stroke (e.g. etiology, vascular territory, management, outcomes).

Statistical Plan:

1) Descriptive statistics to assess overall stroke incidence and patient characteristics
2) Propensity-score matching to generate cohorts of patients taking β blockers with varying degrees of β-1 selectivity
3) Mediation analysis (as data allow) to determine whether hypotension or intraoperative hemorrhage mediate or modulate stroke outcome

Introduction

Perioperative stroke is a potentially devastating complication of noncardiac surgery, with an incidence of up to 2% in high risk populations (Bateman et al, 2009; Mashour et al, 2011). Of note, recent preliminary data indicate that the incidence of perioperative stroke, as detected by magnetic resonance imaging rather than clinical criteria, may be as high as 10% in the noncardiac surgical population (Mrkobrada et al, 2016). Given the prolonged hospital stay, increased disability, and increased mortality associated with this adverse outcome, identification of modifiable risk factors is of paramount importance.

The role of perioperative β adrenergic blockers in the pathogenesis of stroke after noncardiac surgery has been a matter of controversy. In 2008, the PeriOperative Ischemic Evaluation (POISE) trial evaluated the cardioprotective effects of metoprolol in 8351 noncardiac surgery patients and found that patients receiving metoprolol had a significantly higher risk of stroke (hazard ratio 2.17, p=0.005) and death (hazard ratio 1.33, p=0.032) (Devereaux et al, 2008). However, it was argued that the dosing regimen of metoprolol in the POISE trial was not consistent with routine clinical practice (Fleisher and Poldermans, 2008), suggesting that the increased incidence of stroke was a function of study methodology rather than metoprolol pharmacology. In support of this alternative hypothesis, a subsequent observational study found no association between perioperative stroke and the chronic use of β blockers (as a class of drugs) (van Lier et al, 2009). Similarly, a secondary study of the DECREASE trials found that low-dose bisoprolol was not associated with perioperative stroke (van Lier et al, 2010). However, these initial studies subsequent to the POISE trial did not address whether there was a drug-specific effect of preoperative metoprolol (as opposed to β blockers as a class or bisoprolol alone) on the risk of stroke after noncardiac surgery.

In 2013, two studies addressed this question. Mashour et al (2013) conducted a single-center, retrospective observational trial and found that patients taking preoperative metoprolol had a 4-fold unadjusted increase in risk of stroke after noncardiac, nonneurologic surgery; no other β blocker studied had such an association. Importantly, matched cohorts taking either atenolol or metoprolol revealed an increased stroke risk associated with metoprolol. Furthermore, intraoperative metoprolol was associated with a 3-fold increased risk of stroke; there was no such association with patients receiving intraoperative esmolol or labetalol. Ashes et al (2013) also found an increased risk of perioperative stroke in patients taking metoprolol (and atenolol) vs. esmolol. Both of these studies —in conjunction with preclinical data on metoprolol and cerebral oxygenation (Ragoonanan et al, 2009)—suggest that there is a drug-specific effect that increases stroke risk. However, single-center designs and limited outcome numbers preclude firm conclusions that could change clinical practice. If the hypothesis that perioperative stroke varies inversely with β-1 selectivity can be confirmed in a more robust dataset, the impact on patients taking β blockers who are undergoing noncardiac surgery could be enormous. As such, the primary objective of the current study is to assess the relationship of stroke and β-1 selectivity in a noncardiac surgery population taking β blockers, using a large, clinical, multicenter database. We hypothesize that stroke risk will vary inversely with β-1 selectivity.

Additionally, recent data suggest that perioperative stroke is associated with delayed recognition, infrequent thrombolysis, and high rates of mortality and significant disability (Saltman et al, 2015). Prevention efforts have been hindered by the lack of understanding regarding perioperative stroke pathogenesis and etiology. Published case series to date have attempted to classify postoperative stroke subtypes, but classification schemes have been relatively basic (i.e., ischemic vs. hemorrhagic) without detailed subtype reporting (i.e., cardioembolic vs. watershed) (Kikura et al, 2005; Popa et al, 2009).

Thus, understanding the most likely causes of postoperative stroke across a robust, multicenter dataset will help inform subsequent prevention efforts. As such, a secondary objective will be to characterize detailed stroke etiology and subtypes as documented directly from medical charts. Details will also be collected on vascular territory, stroke severity (e.g., NIH Stroke Scale), management, and outcomes.

Methods

This is a retrospective, observational cohort study using the Multicenter Perioperative Outcomes Group (MPOG) database and conducted with Institutional Review Board approval from the University of Michigan, Ann Arbor. In addition, the institutional review board of each member organization also approved aggregation of this limited data set into the (MPOG) centralized data repository. Signed patient consent will be waived as no interventions are involved.

Inclusion criteria

We will examine consecutive adult (age ≥ 18 years) cases of non-cardiac, non-neurologic, and non-cerebrovascular surgeries from five institutions (University of Michigan, University of Virginia, University of Utah, Cleveland Clinic, and Oregon Health and Science University) from January 1, 2004 through the present. Cases from the University of Michigan will only be reviewed after June 31, 2009, given previous postoperative stroke data published from cases before this date (Mashour et al, 2013). Procedures requiring an inpatient stay will be included, will emergency cases.

Exclusion criteria

Cases across various surgical subspecialties will be excluded on the basis of intrinsic procedural risk of intraoperative and perioperative stroke or neurologic deficit. All intracranial neurosurgical cases will be excluded. The following cardiac and vascular procedures, known to have a high stroke risk, will also be excluded: any procedure involving cardiopulmonary bypass, carotid endarterectomies, major vascular cases for vessels above the diaphragm, implantable cardiac defibrillator cases, cardiac dysrhythmia ablation procedures, cases requiring cardioversion, and tamponade evacuations. Otolaryngology cases involving skull base surgery as well as carotid body tumor resections will be excluded. Oral-maxillofacial cases involving penetrating trauma and gunshot wounds to the face and skull will be excluded. All

trauma cases involving multiple organ injury, traumatic brain injury, closed head injuries, and penetrating trauma to the neck will be excluded. Finally, patients with an American Society of Anesthesiologists Physical Status Classification of 5 or 6 were excluded. Procedural exclusions were performed upon the basis of primary procedural ICD9 or professional fee CPT4 code.

Outcome Definition and Assessment

The primary outcome of this study is perioperative stroke, defined as any new-onset cerebrovascular *ischemic* event that occurs during the course of postoperative hospitalization, but no later than 30 days after the surgery. Other surgeries within a 30-day period of the perioperative stroke event were excluded as new index cases. Stroke outcomes will be established by screening for the following ICD9 codes: 433.01, 433.11, 433.21, 433.31, 433.81, 433.91, 434.01, 434.11, and 434.91. Patients coded as having an iatrogenic stroke (ICD-9 CM 997.02) who did not have diagnostic codes indicating hemorrhage (ICD-9 CM 430-432) were also considered to have had a perioperative ischemic stroke. Cases that screened positively for stroke based on ICD9 codes underwent further individual analysis to confirm stroke diagnosis with clinical and/or neuroradiologic evidence.

β blocker exposure

To identify a patient's preoperative medication regimen, the detailed medication history documented in the perioperative EHR will be used. The appendix lists the specific MPOG concepts that will be extracted. Six specific chronic β blockade agents will be evaluated: metoprolol, atenolol, bisoprolol, carvedilol, labetalol, and propranolol. The latter three will be examined as data volume allows. Compliance with β blockade continuation at different sites will be assessed where possible, with accompanying sensitivity analysis.

Confounder and mediator variables

Comorbidity burden may differ among patients in different beta-blocker subtype cohorts, leading to bias. Therefore, we will extract comorbidity data based on association with stroke risk for patients using ICD-9 codes and preoperative electronic health record comorbidity documentation. Specific comorbidities to be assessed include: coronary artery disease (CAD), cerebrovascular disease (e.g, stroke history, TIA history, carotid artery stenosis), atrial fibrillation, valvular disease (e.g., aortic stenosis, aortic regurgitation), hypertension, diabetes, renal failure, chronic obstructive pulmonary disease, tobacco use, and congestive heart failure.

Intraoperative beta-blockers to be assessed include metoprolol, esmolol, labetalol, and propranolol.

Lastly, since intraoperative hemodynamics may affect stroke risk, we will examine the following biologically relevant variables: hypotension, major hemorrhage, and bradycardia. Blood pressure will be assessed by analyzing number of minutes spent with MAP below 55, MAP of at least 55 but less than 60, and MAP of at least 60 but less than 65. Reference blood pressure values will then be minutes with MAP 65 and greater. Logistic regression models will then be constructed with stroke the depending outcome of interest and time spent in each blood pressure strata incorporated as independent variables (Walsh et al, 2013). Major hemorrhage will be defined by the surrogates of transfusion of >4 units of packed red blood cells or whole blood (a value based on Kamel et al, 2012), more than 1000 ml of salvaged blood, an estimated blood loss of greater than 2000 ml, or intraoperative nadir hematocrit below 20%. Bradycardia, which can result from beta-blocker administration, will also be evaluated. Heart rate will also be assessed in the same logistic regression strategy, using time spent with heart rates below 50 and between 51-60 beats per minute as independent variables.

Power Analysis

With four groups (representing the control cohort and preoperative metoprolol, atenolol, and bisoprolol patient cohorts), a total sample of 9020 subjects achieves 80% power to detect a linear trend using a two-sided Z test with continuity correction and a significance level of 0.05 obtained from these 4 groups. Additional post-hoc power analyses will be conducted based on data availability for other beta-blocker cohorts.

Statistical Analysis

First, stroke incidence (as defined in the *Outcome Definition and Assessment* section) and patient characteristics in the overall cohort and for each beta-blocker subtype cohort will be summarized via descriptive statistics. Categorical variables will be described via percentages and quantitative variables will be described via means and standard deviations, as appropriate.

Next, propensity scores will be calculated to estimate the effect of receiving one of the four beta-blocker treatments preoperatively: control, preoperative metoprolol, atenolol, and bisoprolol. Preoperative comorbidities, stroke risk factors, and preoperative beta blockers will be included in the model. Stroke incidence will be compared across the matched groups.

In order to account for potential confounding of beta-blockers given preoperatively and intraoperatively, we will fit a marginal structural model using inverse-probability-of-treatment weight (IPTW). This will also be a two-step method where weights will be first calculated, and then used in a logistic regression model with the stroke outcome as defined in the *Outcome Definition and Assessment* section. This model will adjust for preoperative comorbidities, stroke risk factors, and intraoperative

beta-blockers. Mediation analysis will also be performed, as possible, to assess for indirect effects attributable to intraoperative hypotension, bradycardia, or major hemorrhage.

As a secondary aim, we will perform explanatory analyses (using descriptive statistics) to understand characteristics of postoperative stroke. These will include examining etiology, vascular territory, management, and outcomes as available data allows.

Data Request:

In addition to the variables listed in the standardized view request, there are specific intraoperative and postoperative data elements required for analysis.

The following MPOG preoperative concepts have been identified as risk factors for perioperative stroke and are therefore pertinent to this study:

70024: cardiac arrhythmia
70026: congestive heart failure
70027: coronary artery disease
70031: hypertension
70042: valvular disease
70046: diabetes
70060: renal failure
70086: cerebrovascular diseases
70088: cerebrovascular accident
70115: chronic obstructive pulmonary disease
70128: tobacco history

Exposure to preoperative β blockade will be assessed by reviewing the following data elements from the preoperative history and physical:

70077: General - Medications – Current
71130: General - Medications Detail – Name
71210: General - Medications - Home
70075: β blocker
70305: β blocker continued (to assess for compliance)

The MPOG concepts listed below will be used to identify administration of specific agents intraoperatively as either a bolus or infusion.

10180: esmolol
10242: labetalol
10298: metoprolol
10379: propranolol

The total amount of

10499: estimated blood loss
10489: PRBCs autologous

10490: PRBCs homologous
10491: whole blood autologous
10496 SALVAGED BLOOD (CELLSAVER)

The follow mpog concepts will be used to identify intraoperative hypotension, bradycardia, and nadir hematocrit
3025: BP mean non-invasive
3014: BP sys non-invasive
3040: BP mean arterial line
3011: BP sys invasive unspecified site
3005: EKG pulse rate

3435 POC - hematocrit spun
3450 POC - Coulter counter - Hematocrit
5006 Formal lab - Hematocrit

References

Ashes C, Judelman S, Wijeysundera DN, et al. Selective beta1-antagonism with bisoprolol is associated with fewer postoperative strokes than atenolol or metoprolol: a single-center cohort study of 44,092 consecutive patients. *Anesthesiology* 2013;**119**:777-787

Bateman BT, Schumacher HC, Wang S, et al. Perioperative acute ischemic stroke in noncardiac and nonvascular surgery: incidence, risk factors, and outcomes. *Anesthesiology* 2009;**110**:231-238.

Bijker JB, Persoon S, Peelen LM, et al. Intraoperative hypotension and perioperative ischemic stroke after general surgery: a nested case-control study. *Anesthesiology* 2012;**116**:658-664.

Devereaux PJ, Yang H, Yusuf S, et al. Effects of extended-release metoprolol succinate in patients undergoing non-cardiac surgery (POISE trial): a randomised controlled trial. *Lancet* 2008;**371**:1839-1847.

Fleisher LA, Poldermans D: Perioperative beta blockade: where do we go from here? *Lancet* 2008;**371**:1813-4

Kamel H, Johnston SC, Kirkham JC, et al. Association between major perioperative hemorrhage and stroke or Q-wave myocardial infarction. *Circulation* 2012;**126**:207-212.

Kikura M, Takada T, and Sato S. Preexisting morbidity as an independent risk factor for perioperative acute thromboembolism syndrome. *Arch Surg* 2005;**140**:1210-7.

Mashour GA, Shanks AM, Kheterpal S. Perioperative stroke and associated mortality after noncardiac, nonneurologic surgery. *Anesthesiology* 2011;**114**:1289-1296.

Mashour GA, Sharifpour M, Freundlich RE, et al. Perioperative Metoprolol and Risk of Stroke after Noncardiac Surgery. *Anesthesiology* 2013. *In Press*

Mrkobrada M, Hill MD, Chan MT, et al. Covert stroke after non-cardiac surgery: a prospective cohort study. *Br J Anaesth*. 2016;**117**:191-7

Popa AS, Rainstein AA, Huddleston PM, Larson DR, Gullerud RE, Huddleston JM. Predictors of ischemic stroke after hip operation: a population-based study. *J Hosp Med* 2009;**4**:298-303.

Ragoonanan TE, Beattie WS, Mazer CD, et al. Metoprolol reduces cerebral tissue oxygen tension after acute hemodilution in rats. *Anesthesiology* 2009;**111**:988-1000.

Saltman AP, Silver FL, Fang J, Stamplecoski M, Kapral MK. Care and outcommes of patietns with in hospital stroke. *JAMA Neurol* 2015;**72**:749-55.

van Lier F, Schouten O, van Domburg RT, et al. Effect of chronic beta-blocker use on stroke after noncardiac surgery. *Am J Cardiol* 2009;**104**:429-433.

van Lier F, Schouten O, Hoeks SE, et al. Impact of prophylactic beta-blocker therapy to prevent stroke after noncardiac surgery. *Am J Cardiol* 2010;**105**:43-47.