An international prospective cohort study evaluating major vascular complications among patients undergoing noncardiac surgery: The VISION Pilot Study

ABSTRACT

Objectives: Among patients undergoing noncardiac surgery, our objectives were to: 1) determine the feasibility of undertaking a large international cohort study; 2) estimate the current incidence of major perioperative vascular events; 3) compare the observed event rates to the expected event rates according to the Revised Cardiac Risk Index; and 4) provide an estimate of the proportion of myocardial infarctions that may go undetected without perioperative troponin monitoring.

Design: An international prospective cohort pilot study.

Participants: Patients undergoing noncardiac surgery who were ≥ 45 years of age and receiving a general or regional anesthetic.

Measurements: Patients had a Roche fourth-generation Elecsys troponin T measurement collected 6 to 12 hours postoperatively and on the first, second, and third days after surgery.

Results: We recruited 432 patients across five hospitals in Canada, Hong Kong, Italy, Colombia, and Brazil. During the first 30 days after surgery 6.3% (99% CI, 3.9-10.0) of the patients suffered a major vascular event (10 vascular deaths, 16 nonfatal myocardial infarctions, and 1 nonfatal stroke). The observed event rate was increased 6 fold compared to the event rate expected from the Revised Cardiac Risk Index (RCRI). Of the 18 patients who suffered a myocardial infarction, only 3 (16.7%) patients experienced chest discomfort and 12 (66.7%) had no clinical symptoms or signs to suggest myocardial infarction.

Conclusions: This study suggests that major perioperative vascular events are common, that the RCRI underestimates risk, and that monitoring troponins after surgery can assist physicians to avoid missing myocardial infarction. These results underscore the need for a large international prospective cohort study.

INTRODUCTION

Because noncardiac surgery continues to make important advances in treating diseases and improving quality of life, more patients are undergoing noncardiac surgery. Annually, approximately 200 million adults worldwide undergo major noncardiac surgery.[1,2] Despite its benefits, noncardiac surgery is associated with adverse vascular events (including vascular death, nonfatal myocardial infarction, nonfatal cardiac arrest, and nonfatal stroke).[2]

The increase in elderly patients undergoing surgery, the change in the invasiveness of some surgical interventions, and the limitations of previous research (e.g., dated information, focus on select high-risk groups, single centre studies), highlight uncertainty about the current incidence of major vascular events among patients undergoing noncardiac surgery.[3] Accurate information about major vascular events associated with noncardiac surgery is necessary to inform clinicians, administrators, and granting agencies about resources required to confront this problem.

Further, uncertainty exists regarding the optimal clinical risk estimation model for predicting major vascular events in patients undergoing noncardiac surgery.[4] Previous risk modeling studies were underpowered and most studies were conducted in a single centre university hospital.[3] Accurate risk estimation is essential to facilitate informed patient and physician decision-making regarding the appropriateness of noncardiac surgery and to triage patients to the most appropriate care after surgery.

There is promising but inconclusive preliminary evidence that troponin measurements after surgery can help physicians avoid missing perioperative myocardial infarction.[5] If monitoring troponins after noncardiac surgery assists physicians in detecting perioperative

myocardial infarction that would otherwise go undetected, troponin screening could facilitate appropriate and timely interventions.

We undertook a pilot study with the following objectives: 1) to determine the feasibility of conducting a large international prospective cohort study to address these uncertainties; 2) to estimate the current incidence of major vascular events in patients undergoing noncardiac surgery; 3) to compare the observed event rates to the expected event rates according to the Revised Cardiac Risk Index;[6] and 4) to provide an estimate of the proportion of perioperative myocardial infarctions that may go undetected without troponin monitoring after surgery.

METHODS

Study Design and Eligibility Criteria

We conducted a prospective cohort study of patients undergoing noncardiac surgery. The Vascular events In noncardiac Surgery patIents cOhort evaluatioN (VISION) Pilot Study was performed at five centers: the Hamilton Health Sciences McMaster University Medical Centre (Canada), the Prince of Wales Hospital (Hong Kong), the Italian National Cancer Institute "Regina Elena" (Italy), the Hospital Universitario de Santander (Colombia), and the Hospital de Clinicas de Porto Alegre (Brazil). Patients who underwent noncardiac surgery, were $\geq$ 45 years of age, and received a general or regional anesthetic (plexus block, spinal, or epidural) met the inclusion criteria. Patients for whom we could not obtain consent preoperatively (e.g., some emergent surgical cases) were included if research personnel obtained consent within the first 24 hours after their surgery. We excluded patients receiving only local or topical anesthesia, those

not requiring at least an overnight hospital admission postoperatively, patients previously enrolled in the VISION Pilot Study, and patients who did not consent to participate.

Patient Recruitment

Research personnel screened the daily patient list in the preoperative assessment clinic to identify eligible patients undergoing elective surgery. To identify eligible patients admitted through the emergency department and those who did not attend the preoperative assessment clinic, research personnel screened daily surgical lists, surgical lists from the previous day, patient lists on surgical wards and in intensive care units, and patients in the preoperative holding area. Research personnel approached patients (or their families) who fulfilled the eligibility criteria to obtain written informed consent.

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Data Collection, Monitoring, and Follow-up

Research personnel interviewed and examined patients and reviewed their charts to obtain information on potential predictors of major perioperative vascular events, including risk factors from the Revised Cardiac Risk Index.[6] Patients had blood collected to measure a Roche fourth-generation Elecsys troponin T assay 6 to 12 hours postoperatively and on the first, second, and third days after surgery. The coefficient of variation is < 10% at 0.035 μg/L. Based upon guideline recommendations we considered a Troponin T value ≥ 0.04 μg per liter elevated. Patients enrolled between 12 and 24 hours after surgery had a troponin T drawn immediately and continued testing as outlined above. An electrocardiogram (ECG) was undertaken immediately after an elevated troponin measurement was detected. If a troponin T measurement was elevated but the patient had no ECG changes or ischemic signs or symptoms to fulfill the diagnostic

criteria for myocardial infarction, then we recommended the patient undergo an echocardiographic study.

Research personnel followed patients throughout their hospital stay, clinically evaluating them and examining their medical records to ensure caregivers followed study orders and to identify primary and secondary outcomes. We contacted patients by phone at 30 days after surgery; if patients (or their families) indicated that they had experienced an outcome, we contacted their physicians to obtain documentation. Data collection forms and supporting documentation were faxed or entered online from participating centers directly to the iDataFax Management System at the coordinating centre in McMaster University.

Outcomes

Appendix I provides the outcome definitions. For our first objective (to determine the feasibility of conducting a large international cohort study) our primary outcome was achieving ≥ 95% follow-up. For our second and third objectives (to estimate the current incidence of major vascular events and to compare the observed event rates to the expected event rates according to the Revised Cardiac Risk Index) our primary outcome was major vascular events (a composite of vascular death, nonfatal myocardial infarction, nonfatal cardiac arrest, and nonfatal stroke) at 30 days after surgery. Individual secondary outcomes for our second objective included: vascular mortality, myocardial infarction, cardiac arrest, stroke, congestive heart failure, new clinically important atrial fibrillation, and re-hospitalization for vascular reasons at 30 days after surgery.

For our fourth objective (to provide an estimate of the proportion of perioperative myocardial infarctions that may go undetected without perioperative troponin monitoring) our primary outcome at 30 days after surgery was any myocardial infarction that *probably* would

have gone undetected without perioperative troponin monitoring (myocardial infarction without chest discomfort or other symptoms or signs suggesting myocardial infarction), and our secondary outcome was myocardial infarction that *possibly* would have gone undetected without perioperative troponin monitoring (myocardial infarction without chest discomfort but with other symptoms or signs of possible myocardial infarction).

2Two outcome adjudicators independently assessed all major vascular events without knowledge of the patient's vascular risk factors. All disagreements were resolved through a consensus process that required the adjudicators to discuss the reasoning behind their decisions. If disagreement persisted, a third adjudicator made a final decision.

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4Analysis

We determined the proportion of patients suffering a major vascular event and the associated 99% confidence interval. For all patients, we determined the expected number of major vascular events according to the Revised Cardiac Risk Index and calculated the ratio of the observed to the expected number of events and the associated 99% confidence interval. We used a Fisher's exact test to compare the proportion of urgent or emergent patients who underwent surgery on a weekend to the proportion who underwent surgery on a weekday. We used generalized estimating equations for repeated measures to determine if there were statistically significant variations in the usage of various cardiovascular drugs across any of the 4 time periods we evaluated (the week before surgery, within 24 hours prior to surgery, during the first 72 hours after surgery, and at discharge).

5Ethic Considerations

All patients or their families provided written informed consent. The Research Ethics Board at each site approved the protocol prior to patient recruitment.

RESULTS

We recruited 432 patients fulfilling eligibility criteria into the VISION Pilot Study, 17 (3.9%) of whom consented during the first 24 hours after surgery. The patient flow chart for recruitment across all sites is shown in Figure 1. A comparison of the study log with operating room surgical records, and where available hospital computer systems, demonstrated that study personnel approached 85.0% of all potentially eligible patients. Missed patients were primarily elective patients who were rescheduled on short notice, elective patients with the same booking time as many other elective cases, and some patients who underwent weekend surgery. Forty-eight patients refused to participate (10.0% refusal rate).

Table 1 presents the patient characteristics. Seventy-one patients (16.4%) underwent surgery within 72 hours of an acute event (i.e., urgent/emergent surgery). Nineteen patients underwent surgery on a weekend and 12 (63.2%) of these patients met our definition for urgent/emergent surgery, whereas 59 (14.3%) of the 413 patients who underwent surgery on a weekday were in this category ($p<0.001$). Sixty-one (14.1%) patients had a history of coronary artery disease, and 184 (42.6%) patients had a history of hypertension.

Table 2 reports the proportion of patients taking various cardiovascular drugs regularly in the week before surgery, within 24 hours of surgery, at some time during the first 72 hours after surgery, and at hospital discharge. Aspirin and oral anticoagulation therapy demonstrated the greatest decrease in use during the first 72 hours after surgery compared to regular use in the

week prior to surgery. The anesthesia patients received (some patients received more than 1 type of anesthesia) included: general 369 (85.4%) patients, spinal 55 (12.7%) patients, thoracic epidural 35 (8.1%) patients, lumbar epidural 12 (2.8%) patients, and nerve block 12 (2.8%) patients. Patients underwent surgery for a median of 105 minutes (interquartile range [IQR] 70-165).

Three patients withdrew from the study, and we completed our 30-day follow-up on the remaining 429 patients (i.e., 99.3% of patients completed follow-up). The median length of hospital stay was 5.5 days (IQR 3.0-10.0). During the first 30 days after surgery 6.3% (99% CI 3.9-10.0) of the patients suffered a major vascular event (10 vascular deaths, 16 nonfatal myocardial infarctions, and 1 nonfatal stroke). Secondary outcomes included 10 (2.3%) patients who died due to vascular reasons, 18 (4.2%) patients who developed a myocardial infarction (16 nonfatal, 2 fatal), 2 (0.5%) patients who had a stroke (1 nonfatal and 1 fatal), 4 (0.9%) patients who developed congestive heart failure, 7 (1.6%) patients who developed new clinically important atrial fibrillation, and 1 (0.2%) patient who was re-hospitalized for vascular reasons at 30 days after surgery.

Table 3 reports the observed major vascular event rates and the expected major vascular event rates according to the Revised Cardiac Risk Index. Observed event rates were 6 fold higher (99% confidence interval, 3.5-9.7) than the expected event rates according to the Revised Cardiac Risk Index.

The median number of protocol troponin assays measured (maximum of 4 per patient) was 4.0 (IQR 3.0-4.0) per patient. Eighteen patients suffered a myocardial infarction of whom, only 3 (16.7%) experienced chest discomfort and 12 (66.7%) had no clinical symptoms or signs to suggest myocardial infarction. Therefore, probably 12 (66.7%) and possibly 15 (83.3%) of

these myocardial infarctions would have gone undetected without perioperative troponin monitoring.

DISCUSSION

Principal Findings

Among patients ≥ 45 years of age undergoing noncardiac surgery requiring hospital admission, we demonstrated a 6.3% (99% CI 3.9-10.0) event rate for major vascular events during the first 30 days after surgery. In our study, the Revised Cardiac Risk Index substantially underestimated the risk of major perioperative vascular events. Physicians probably would have missed a majority (i.e., 66.7%) of perioperative myocardial infarctions if we had not monitored troponin measurements during the first few days after surgery.

Strengths and Weaknesses of Our Study

Strengths of our study include its reflection of current practice across multiple international hospital sites and the inclusion of patients who underwent urgent emergent surgery and surgery during weekends. Research personnel used a wide variety of approaches to identify eligible patients. Two independent outcome adjudicators, blinded to patients' vascular risk factors, evaluated all major vascular events, and we used a consensus process to resolve disagreements. We achieved 99.3% follow-up at 30 days after surgery.

Our study has several limitations. We enrolled only 432 patients and observed only 27 major vascular events; therefore the findings of this pilot study warrant cautious interpretation. We evaluated the accuracy of the Revised Cardiac Risk Index but were unable to conduct similar

analyses according to other risk indices (e.g., Veterans Affairs Model, Modified Cardiac Risk Index)[7,8] because the original publications did not report the precision of their estimates. Using the data from the original Revised Cardiac Risk Index Study, we previously reported the expected incidence of major perioperative cardiac events (i.e., cardiac death, nonfatal myocardial infarction, and nonfatal cardiac arrest) according to the Revised Cardiac Risk Score.[3] In the VISION Pilot Study our primary outcome included fatal and nonfatal stroke. This increased our observed event rate; however, this only accounts for a small portion (i.e., 2 events) of the difference between our observed event rate (i.e., 27 events) and our expected event rate (i.e., 4.5 events), Table 3.

Our Study in Relation to Other Studies

Considering prior research, the study by Lee and colleagues[6] provides the best estimate of the incidence of major vascular events in unselected adults undergoing noncardiac surgery requiring hospital admission.[3] This study suggests that major perioperative vascular events occur in 1.4% (95% CI 1.0-1.8%) of adults.[3]

Several potential explanations exist for the higher event rate (i.e., 6.3%) in the VISION Pilot Study. First, the patient population may have changed in the time (i.e., > a decade) between the study by Lee et al. and our study. Since then patients with coronary artery disease are living longer and developing conditions that require noncardiac surgery, a higher proportion of elderly patients are now undergoing noncardiac surgery, and some surgical interventions have become less invasive,[3] raising questions regarding the applicability of Lee's results from the late 1980's and early 1990's. Second, we used troponin T whereas Lee et al. used CK-MB in the diagnostic criteria for myocardial infarction. CK-MB is prone to false-positive and false-negative values

for perioperative myocardial infarction.[5] Third, we included emergent surgical cases (8 events occurred in emergent patients), and we considered stroke a major adverse outcome whereas the study by Lee et al. excluded emergent surgical cases, and stroke was not considered as a major vascular event.[6] Our study included data from 5 hospitals in 5 countries, whereas the study by Lee et al. included patients from a single hospital. Finally, our results may represent a chance finding as a consequence of the small sample size.

We are unaware of any prior studies that have compared observed event rates to the expected event rates according to the Revised Cardiac Risk Index. Three prior prospective cohort studies of patients undergoing various noncardiac surgeries who had at least 1 postoperative measurement of a cardiac enzyme or biomarker have evaluated the proportion of perioperative myocardial infarctions with and without symptoms or signs suggestive of myocardial infarction.[9-11] The pooled results from these 3 studies demonstrated that only 16% (95% CI 6-31) of patients who suffered a perioperative myocardial infarction experienced chest discomfort and approximately half (45%, 95% CI 29-62%) had neither chest pain nor any other symptoms or signs to suggest myocardial infarction.[5]

Although these studies demonstrated similar results to the VISION Pilot Study they are limited in that there were only a total of 38 myocardial infarctions and they were restricted to patients with, or at high-risk for, coronary artery disease. These studies are also limited because they used CK-MB in their diagnostic criteria for myocardial infarction, and there were variations across studies regarding monitoring (e.g., 2 studies monitored CK-MB[9,10] and 1 study started monitoring troponin T[11] after enrolling 28% of the patients).

Based on the results of this pilot we have initiated the full scale large international VISION Study. This study is designed to ensure adequate power (i.e., we aim to have at least

720 major vascular events) to allow us to determine the optimal risk model for predicting major perioperative vascular events.

Conclusions

Our results suggest that major perioperative vascular events are more common than previously reported, that the Revised Cardiac Risk Index underestimates risk, and that monitoring troponins after surgery will allow physicians to avoid missing myocardial infarctions. Results from the ongoing VISION Study will further inform these issues.

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Appendix

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