PCRC Proposal Cover Sheet

Title: Do Anesthesiologists Matter?

Principle Investigator: Sachin Kheterpal, MD, MBA

Co-Investigators: Justin Dimick MD MS, John Birkmeyer MD, Mousumi Banerjee PhD, Amy Shanks MS, Kevin K Tremper, PhD, MD and others that are interested

Approved by Mentor: Sachin Kheterpal, MD, MBA

Type of Study: Retrospective

Hypothesis: We hypothesize that the anesthesiology provider is responsible for a measurable proportion of center-level variation in risk adjusted patient outcomes.

Number of Patients/Participants: Approximately 50,000

Power Analysis: For the generalized linear mixed models proposed for this study, there are no closed form equations for calculating sample size. Simulation studies suggest that 100 groups (i.e. anesthesiologists) and group sizes of 30 (i.e. number of patients per anesthesiologist) produce reasonably valid estimates in hierarchical logistic regression models. We expect to have data on approximately 700 anesthesiologists, treating in the range of 10 - 522 patients over the entire study period. Of the 700 anesthesiologists, 81% treated at least 30 patients over the study period. Therefore, we have sufficient sample size to obtain reasonably valid estimates.

Proposed statistical test/analysis: We will stratify by procedural complexity quintiles, and incorporate *center*, *surgeon*, and *patient comorbidities* into models of 30 day morbidity and mortality. After adjusting for these important covariates, we will describe the variation in risk-adjusted outcomes across anesthesiologists. Four major exposure domains must be addressed to optimize isolation of the anesthesiologist effect: *center*, *surgeon*, *patient, and procedural complexity*. We will use a hierarchical logistic regression (generalized linear mixed models with logit link) for this analysis to be completed using SAS.

Resources (Brief summary of resources for data collection, personnel, financial): Mark Dehring will be abstracting the data from the MPOG database. Statistical support provided by Amy Shanks and consultation by Mousumi Banerjee.

Title: Do Anesthesiologists Matter?

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Site: University of Michigan

Introduction

Over 40 million major operative procedures are performed in the US annually.(1) Despite decades of research, perioperative mortality and morbidity remain a major healthcare system cost and detriment to long-term quality of life. More than ten percent of patients experience a significant event such as surgical site infection, reoperation, myocardial infarction, pulmonary embolus, or death.(2) Nearly 100,000 patients die after surgery each year. National data demonstrate a 3-fold variation in risk adjusted surgical morbidity and mortality, suggesting many opportunities for improvement in perioperative care.(3)

Efforts to reduce variation and improve overall quality in surgery have traditionally targeted the operating surgeon, the hospital, and hospital staff involved in perioperative care. For example, professional organizations in surgery are promoting national clinical registries such as the American College of Surgeons–National Surgical Quality Improvement Program (ACS-NSQIP) and Society of Thoracic Surgeons (STS) Adult Cardiac Database for tracking surgical outcomes and providing detailed performance feedback to individual surgeons. At the hospital level, the Centers for Medicare and Medicaid Services (CMS) and a number of states have initiated a number of public reporting initiatives aimed at making hospitals more accountable for their outcomes and incentivizing quality improvement.

Although ongoing initiatives are focusing on the surgeon and hospital, anesthesiology is obviously an important part of the surgical episode. Historically, anesthesiology has focused its efforts in reducing the risk of catastrophic, albeit infrequent, events leading to immediate morbidity and mortality, such as unrecognized esophageal intubation, failed airway access, and medication errors. The epidemiology of anesthetic mishaps suggests that these efforts have been successful. For example, the field has observed a decrease in anesthesia-caused mortality from 1 in 4,000 just 40 years ago to 1 in 200,000 today and has been hailed as a patient safety pioneer.(4) Despite this success, there is growing recognition that anesthesiologists may play a substantial role in the risk of much more common adverse events after surgery. They enable the surgical procedure using potent medications that inhibit consciousness, perception of pain, or musculoskeletal response within a narrow therapeutic window. The anesthesiologist is responsible for maintaining the patient's cardiopulmonary, renal, and neurologic systems in a safe, yet dynamic zone of equilibrium despite the surgical injury and the anesthetic.

There is emerging awareness of the anesthesiologist's potential value in reducing postoperative complications. The anesthetic management of the intraoperative injury, stress, and inflammation may modify broad ranging postoperative outcomes such as myocardial infarction, acute kidney injury, healthcare associated infections, venous thromboembolism, cancer progression, need for reoperation, and cognitive decline.(5)The Surgical Care Improvement Project's three clinical focus areas, surgical site infections (SSI), myocardial infarction, and venous thromboembolism, are dependent on the anesthesiologist for intraoperative interventions: active warming and administration of antibiotics, beta-blockers, or anticoagulants. More provocatively, the use of peripheral nerve blockade or neuraxial anesthesia in lieu of general anesthesia has been demonstrated to improve cancer-free survival one year after prostate and breast cancer surgery.(6, 7) We have used our single-center data to show that even 10 minutes of intraoperative hypotension are associated with increased risk of postoperative acute kidney injury.(8) Intraoperative hypotension has also been implicated with an increase in surgical site infections in case-control analyses.(9)

Therefore our goal with this study is to isolate the proportion of outcome variation that is attributable to the anesthesiologist after adjusting for the center (site), surgeon, and patient covariates. Using a national dataset integrating robust preoperative risk stratification, 30-day outcomes, and intraoperative anesthetic management we will evaluate the impact of anesthesiologists on a composite 30-day morbidity and mortality outcome. We hypothesize that the anesthesiology provider is responsible for a measurable proportion of center-level variation in risk adjusted patient outcomes.

Materials and Methods

Institutional review board was obtained for this multicenter, retrospective observational study (University of Michigan, Ann Arbor, Michigan). Because no care interventions were involved and all protected health information was removed prior to analysis, patient consent was waived. All operations performed between 2004 to 2012 at eight participating centers within the multicenter perioperative outcome group (MPOG) were included for analysis. The eight participating centers that will be included for this analysis are: Columbia University, Massachusetts General Hospital, Oregon Health Science University, University of Michigan, University of Tennessee at Knoxville, University of Utah, University of Virginia Health System, Washington University, and Vanderbilt University.

The MPOG database includes data from anesthesia information systems (AIMS), American College of Surgeons – National Surgical Quality Improvement Program (ACS-NSQIP), and 1 year all-cause mortality from the social security death master file. These data sources complement each other and create a robust set of data elements for risk adjustment, provider details, intraoperative domains of practice, and outcomes. The AIMS data includes not only the detailed intraoperative anesthesia record, but also a structured preoperative assessment, laboratory values, surgeon and anesthesiology provider elements, surgical diagnoses, and surgical procedural details. ACS-NSQIP data will be used for risk adjustment, procedural details, and 30-day postoperative outcome data. Trained surgical clinical nurse reviewers undergo rigorous training on data element definitions and prospectively collect all data. Periodic inter-rater reliability tests are performed at all sites by an external reviewer. Recent data demonstrate an exceptional < 1.4% discordance rate for ACS-NSQIP data element extraction.(10) Given the rich, prospectively collected clinical data with the AIMS and ACS-NSQIP data sources, the proposal does not rely on administrative data elements for primary outcomes. However, 1 year all-cause mortality will be derived for each patient using a combination of hospital records and linking each patient record with the social security death master file.

Within the MPOG database, there are approximately 50,000 records that are linked with AIMS and ACS-NSQIP data. ACS-NSQIP specifically focuses on a sampling methodology that is focused on adult patients undergoing either elective or emergency general of vascular operations. The most commonly performed procedures within the MPOG database based on the ACS-NSQIP procedures are listed in table 1. For each MPOG record that meets the inclusion criteria of an adult patient with valid AIMS and ACS-NSQIP data and is a surgical case that has more than 100 cases within the MPOG dataset, the following data will be abstracted; center (specific institutional site uniquely coded), anesthesia provider, surgeon, and specific patient covariates. The center will be uniquely coded within the MPOG's honest broker system and no institutional names will be supplied to the statistician for analysis. For each MPOG record, the anesthesiology attending that was primarily responsible for that patient's intraoperative care is encoded using a unique national identifier. This is completed at each individual MPOG site prior to submitting data into the centralized MPOG dataset. For cases in which there were multiple anesthesiology attendings signed into the case, if a majority (≥51%) of the surgical duration was by one attending, that would be considered the primary anesthesiology provider.

The primary outcome modeled will be the composite 30-day mortality and morbidity outcome using ACS-NSQIP data. This outcome includes all twenty-three morbidity events and 30-day mortality. The twenty three outcomes grouped into categories are available for the proposed analyses: *wound* (superficial, deep, or organ space surgical site infection, fascial dehiscence), *respiratory* (pneumonia, reintubation, pulmonary embolism, prolonged ventilator dependence), *renal* (renal insufficiency, dialysis, urinary tract infection, *neurologic* (stroke, coma, peripheral nerve injury), *cardiac* (cardiac arrest, myocardial infarction), *surgical events* (bleeding requiring aggressive transfusion, graft/flap failure, deep venous thrombosis, sepsis, septic shock), and *disposition* (reoperation, all-cause mortality). Detailed definitions are used for each outcome and exclude patients with pre-existing conditions that render the outcome nonsensical (ie, patient with preoperative dialysis requirements will not have the outcome of acute renal failure requiring dialysis). In aggregate, approximately 17% of patients in the ACS-NSQIP experience a 30-day adverse event. It is plausible that the anesthesiologist affects certain outcomes more than others. The use of a single composite outcome may not elucidate these relationships. As a secondary analysis, four morbidity groups will be analyzed in distinct models: surgical site (superficial, deep, or organ space surgical site infection, fascial dehiscence, and graft/flap failure), healthcare associated infections (pneumonia, sepsis, septic shock, and urinary tract infection), cardiovascular (cardiac arrest, myocardial infarction, stroke, venous thromboembolism), and other organ-system malfunction (reintubation, prolonged ventilator dependence, renal insufficiency, dialysis).

Statistical Analysis

This macro-level analysis will include all patients in the MPOG database that have combined AIMS and ACS-NSQIP data. We will stratify by procedural complexity quintiles, and incorporate *center*, *surgeon*, and *patient comorbidities* into models of 30 day morbidity and mortality. After adjusting for these important covariates, we will describe the variation in risk-adjusted outcomes across anesthesiologists. Four major exposure domains must be addressed to optimize isolation of the anesthesiologist effect: *center*, *surgeon*, *patient, and procedural complexity*. Each of these domains has been studied extensively. (11-18) We will use a hierarchical logistic regression (generalized linear mixed models with logit link) for this analysis to be completed using SAS.

Center effect (institutional site) will be addressed by the use of fixed effects in the model. Center details such as volume and practice type will not be incorporated into the model because they are not the focus of this proposal. Approximately 500 surgeons are represented in this patient population. A primary surgeon will be incorporated into the model as a random effect. Although our previous research has evaluated the components underlying provider effect (experience, volume, certification), this proposal is focused on the anesthesiologist effect and will not decompose the surgeon effect beyond the provider level. Based upon previous work, three demographic variables (age, sex, body mass index), ASA physical status classification, acuity (emergent vs non emergent), 42 ACS-NSQIP comorbidity elements, and three preoperative laboratory values (albumin, hemoglobin, creatinine) will be incorporated into the model as fixed effects covariates. The forty two data elements establish the presence or absence of a variety of clinical conditions *prior* to the operative intervention. The elements include general (diabetes, smoking and alcohol consumption), pulmonary (chronic obstructive pulmonary disease, current pneumonia), gastrointestinal (ascites, varices), cardiovascular (angina, congestive failure, coronary artery stent, peripheral vascular occlusive disease, renal, central nervous system (sensorium, stroke, transient ischemia attacks), and conditions specifically required for surgical outcome risk adjustment (preoperative wound classification, disseminated cancer, preoperative sepsis, and unintentional 10% weight loss in six months prior to surgery). The procedures included in this dataset have a wide range of composite morbidity rates, ranging from 3% for inguinal hernia repair to 26% for colectomy, with an overall morbidity/mortality rate of 17%. It is plausible that the anesthesiologist impacts morbidity for complicated procedures requiring many intraoperative interventions while he does not impact simple procedures with limited complexity and composite morbidity. We will stratify the analysis based upon quintiles of procedure risk. In combination with procedural complexity, these patient variables have previously accounted for 80% of surgical outcome variation.(19)

A hierarchical logistic regression model (generalized linear mixed model with logit link) will be used to account for clustering of patients within anesthesiologists. Within each procedure complexity quintile, we will perform a hierarchical logistic regression analysis with the dichotomous composite 30-day mortality and morbidity as the outcome, adjusting for patient (fixed), surgeon (random), and center (fixed) effects. The dataset includes procedures spanning more than seven years, so a dummy variable for year of procedure will also be incorporated as a fixed effect.

The model will also include a random anesthesiologist-specific intercept to account for the clustering of patients within anesthesiologists. Let Yijk =1, if the jth patient treated by the ith anesthesiologist and kth surgeon suffered an adverse event within 30 days of surgery, and Yijk = 0 otherwise. The probability of an adverse event for the jth patient treated by the ith anesthesiologist and kth surgeon can then be modeled as follows:

Level 1: between-patients (within anesthesiologist): $\text{logit}(P(Y_{ijk}=1)) = \mu_{0i} + \gamma_{0k} + \underline{\theta}' X_{ijk}$

Level 2: between-anesthesiologists: $\mu_{0i} = \beta_{00} + \beta_{0i}$
Combined model: $\text{logit}(P(Y_{ijk} = 1)) = \beta_{00} + \beta_{0i} + \gamma_{0k} + \underline{\theta}' X_{ijk}$

where β_{00} is the population-averaged log-odds of an adverse event, β_{0i} is the anesthesiologist-specific random effect, assumed to follow a normal distribution with mean zero and variance σ^2_{anes}, γ_{0k} is an additive random effect corresponding to surgeon, $\underline{X}_{ijk}$ is the matrix of patient, procedural, year, and center covariates, and $\underline{\theta}$ is the corresponding vector of fixed effects representing changes in the log-odds of an adverse effect corresponding to each unit change in the covariate values. Model estimates will be obtained using likelihood based approach (marginal or penalized quasi-likelihood). Alternatively, we will also employ a fully Bayesian approach using Markov Chain Monte Carlo (MCMC).

We shall calculate adjusted odds ratios and the corresponding 95% confidence intervals for each of the fixed effect covariates (center, patient, procedural, and year). Model comparison will be performed using AIC and BIC. We will report the estimated variance components from the above model. In addition, we will report the intra-cluster correlation (ICC) as an estimate of the proportion of outcome variation attributable to the anesthesiologist level. In order to assess if the anesthesiologist effect is more or less pronounced for specific complications, secondary analyses will repeat the above modeling strategy for each of the four specific morbidity groups described: surgical site, healthcare associated infection, cardiovascular, and other organ-system malfunction.

Sample Size

For the generalized linear mixed models proposed for this study, there are no closed form equations for calculating sample size. Simulation studies suggest that 100 groups (i.e. anesthesiologists) and group sizes of 30 (i.e. number of patients per anesthesiologist) produce reasonably valid estimates in hierarchical logistic regression models.(20,21) We expect to have data on approximately 700 anesthesiologists, treating in the range of 10 - 522 patients over the entire study period. Of the 700 anesthesiologists, 81% treated at least 30 patients over the study period. Therefore, we have sufficient sample size to obtain reasonably valid estimates.

Additionally, we conducted a Monte-Carlo simulation analysis varying the distributions of the practice domain variables to develop estimates of our power to detect significant differences in composite 30-day mortality and morbidity rates. We assumed that the baseline event rate across procedures is 17%. In our power analyses we explicitly accounted for the clustering of patients within anesthesiologists by varying the intra-cluster correlation coefficient ρ between 0.01 and 0.2.(22, 23) These values reflect the range of ICCs observed in other large studies with patient clustering.(24) Based on our simulations, we have determined that with 700 anesthesiologists, and 30 patients per anesthesiologist (conservative estimate), we will have 90% power using a two-sided test at α=0.05 to detect odds ratios between 1.13 (best case scenario) and 1.52 (worst case scenario) as statistically significant, assuming intra-cluster correlations in the range of 0.01 to 0.2.

Limitations

There are several foreseeable limitations to this study: lack of generalizability, ACS-NSQIP data quality, outcome measures, and multilevel modeling. Despite the large sample size and multicenter nature of this dataset, the ACS-NSQIP collection methodology at participating centers is limited to general and vascular surgery patients. A diverse range of procedures is included, but it is feasible that conclusions regarding the role of the anesthesiologist may not be readily generalizable to other common surgical specialties such as orthopedics, obstetrics, gynecology, urology, and cardiac surgery. In the interim, the MPOG database includes hundreds of thousands of orthopedic, obstetric, gynecologic, and urologic surgeries. Previous analyses have demonstrated that although the detailed ACS-NSQIP comorbidity collection process improves model discriminating power, the use of readily available risk stratification elements from the AIMS may be sufficient for initial analyses attempting to validate the generalizability of our findings: age, sex, ASA physical status, albumin, hemoglobin, creatinine, baseline blood pressure, and procedural complexity.(19, 25, 26) The generalizability of our findings to all care settings, such as rural hospital, may also be limited due to the absence of rural facility data in the current MPOG dataset.

Although the ACS-NSQIP dataset is rigorously collected and demonstrates < 1.4% inter-rater reliability errors, issues with missing data and data quality must be considered in any observational secondary analysis. For all variables included in the analysis, we will evaluate the proportion of missing data and concordance between data sources (AIMS and ACS-NSQIP) for shared data elements (demographics, ASA status, body mass index, height, weight, laboratory values). The ACS-NSQIP data elements are collected prospectively by trained clinical data collectors and are a vast improvement over administrative, retrospective collected data that dominate current structure-process-outcomes analyses. Based upon the missing data proportion and distribution, we will either exclude the cases or perform multiple imputations (if not missing at random).

Although the ACS-NSQIP dataset includes all major organ system complications and mortality, it is conceivable that the anesthesiologist affects important surgical outcomes not measured in the ACS-NSQIP dataset, resulting in an underestimation of anesthesiologist impact. For example, although wound complications such as dehiscence and surgical site infections are available, more intermediate outcomes such as time to first oral intake are missing. For oncologic procedures, there are no data regarding cancer progression or recurrence, although a link to anesthesia technique has been proposed. The use of 1 year mortality as a surrogate for cancer progression may be a strategy to mitigate this issue. For oncologic surgical procedures, we will perform a sensitivity analysis by incorporating 1-year all-cause mortality into the primary morbidity-mortality outcome to assess whether the anesthesiologist impact increases or decrease.

The ideal hierarchical logistic regression model for this proposal would create three levels of clustering: 1) patient, 2) surgeons, and 3) anesthesiologists. However, creation of a surgeon level (nested within anesthesiologists) in the hierarchical model is challenging because of the sparsity of data introduced with the additional level, which may potentially lead to model convergence issues. As such, we will incorporate surgeon at the same level as patient through an additive random effect for the surgeon.

Table 1: Sample size of common procedures in the MPOG – ACS-NSQIP dataset

Procedure category (CPT codes)	N	Composite 30-day morbidity %	30-day mortality %
Cholecystecomy (47480, 47560, 47425, 47579, 47600, 47562)	5,562	5.3	0.6
Colectomy, with or without colostomy (44139 – 44147, 44150 – 44160, 44213, 44320, 44322, 44340, 44345, 44346, 44604, 44605, 44615, 44620 ,44625, 44626)	5,073	26.7	4.2
Excisional breast biopsy (19110, 19112, 19120, 19125, 19126)	4,871	3.1	0.1
Repair of ventral, incisional, or umbilical hernia (49491, 49560,49561, 49565, 49566, 49568, 49570, 49572, 49605)	4,506	6.6	0.4
Appendectomy (44900, 44950, 44955, 44960, 44970, 44979)	3,627	4.2	0.2
Repair of inguinal or femoral hernia (49505, 49507, 49520, 49521, 49525, 49550, 49553, 49555, 49557, 49650, 49651)	3,480	1.6	0.2
Gastric bypass (43644, 43645, 43770, 43771, 43772, 43773, 43774, 43842, 43843, 43845, 43846, 43847, 43848)	3,169	5.1	0.2
Thrombectomy or bypass of peripheral artery (35302, 35303, 35305, 35321, 35371, 35372, 35381, 35521, 35522, 35525, 35533, 35556, 35558, 35565, 35566, 35571, 35572, 35583, 35585, 35587, 35621, 35623, 35654, 35656, 35661)	2,873	17.3	3.2
Carotid endarterectomy (35390, 35501, 35506, 35510, 35601, 35606, 35626, 35691, 35694, 35701, 35800, 60600)	1,624	5.8	0.6
Abdominal aortic aneurysm (34800, 34802, 34803, 34804, 34805, 34825, 34830, 34831, 34832, 35082, 35092)	1,354	25.4	27.2

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