Predictors of perioperative pulmonary complications in non-cardiac surgeries

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Introduction

Perioperative pulmonary complications (PPCs) are a common cause of major mortality and morbidity. Studies from the 1990s demonstrated that 5 – 10% of unselected surgical patients and 9 – 40% of patients having abdominal surgery suffered pulmonary complications in the post-operative period.[1,7] Recent literature has confirmed that despite increased awareness of pulmonary complications, 5-10% of surgical patients continue to suffer from PPC.[8] (add in Canet refernce) For patients already suffering from chronic respiratory disease, 26% develop pulmonary complications.[1,6 9]

Post-operative respiratory failure, one form of PPC, is clearly associated with short and long-term mortality and cost.[10-15] During the first six days following surgery, nearly 25% of patient deaths relate to pulmonary complications.[1,5] Khuri and colleagues reported the 5 and 10 year mortality following post-operative respiratory failure to be greater than 50% and 70% respectively.[10,15] Johnson, et al., found a 30-day mortality of 26.5% following post-operative respiratory failure.[10] Sigl, et al., found that the relative risk of in-hospital death was increased 77-fold over baseline by a post-operative pulmonary complication.[8] Ramachandran, et al., found that unanticipated intubations within 72 hours after surgery were associated with a 9-fold increase in relative risk of mortality.[9] With a median incremental hospital cost of $62,000, respiratory complications have a greater cost impact than thromboembolic, cardiovascular, or infectious postoperative complications.

Accordingly, for both patient safety and economic efficiency reasons, it is important to understand what factors and especially what modifiable factors impact the likelihood of PPCs. Despite the large body of work regarding PPC, a notable void has

been a robust analysis of intraoperative anesthetic management and physiology that may be associated with an increased risk of PPC. The impact of intraoperative anesthetic management on long term outcomes is becoming increasingly clear. Anesthesia technique, volume management, and hemodynamic management being may be related to changes in postoperative cancer progression, perioperative cardiac events, and cognitive dysfunction.(Sessler Anesthesiology 2010) However, the relationship between intraoperative management and PPC has never been explored for patients undergoing non-cardiothoracic surgery.

This study was undertaken to expand the understanding of the relationship between intraoperative management and PPC. By integrating multicenter, risk-adjusted, prospectively collected 30-day outcomes from the American College of Surgeons National Quality Improvement Program database with detailed minute-to-minute physiology and intervention data from anesthesia information management systems (AIMS) we hoped to better understand the impact of variables that are anesthesia specific, intraoperative, and believed to be clinically relevant on the basis of other research and biological mechanisms.[17] We hypothesized that fluid management, lung peak airway pressures, use of PEEP, respiratory rate, hypotension, and use of vasopressors may be related to PPC. (References)

Materials and Methods

This research was conducted as a retrospective, observational study at multiple academic, tertiary care centers. Institutional review board approval was obtained (University of Michigan, Ann Arbor), and patient consent was waived as no care interventions were performed and patient identifiers were not used. Data was collected over a seven year period from 2005 to 2011. The data was collected via two systems: AIMS and the National Surgical Quality Improvement Program (ACS-NSQIP). The AIMS data of multiple institutions was consolidated via a data repository known as the Multicenter Perioperative Outcomes Group (MPOG) database.(Kheterpal, Anesthesiology Clinics of North America 2010) The NSQIP data was compiled using the methods of NSQIP which have been described in detail in other publications. (Khuri JACS).

Patient Population

Patients included in this study were adults (age >= 18 years) who underwent major general or vascular procedures at one of three academic hospitals in the United States. As in the NSQIP methodology, major operations were defined as those involving general, spinal, or epidural anesthesia.

Outpatient surgeries were excluded. Patients were excluded if they had undergone operations within the previous 30-day period, had pre-existing ventilator dependence, pneumonia, quadriplegia, coma, or sepsis.

Outcomes

The primary outcome evaluated was a composite PPC of postoperative respiratory failure (PRF) or postoperative pneumonia (PP) within 30 days of surgery. Both outcomes were collected via the ACS-NSQIP database. Postoperative respiratory failure was defined as unplanned intubation for cardiorespiratory failure or prolonged postoperative ventilation > 48 hours. Postoperative pneumonia must meet one of the following TWO criteria:

Criterion 1: Rales or dullness to percussion on physical examination of chest AND any
of the following:

a. New onset of purulent sputum or change in character of sputum

b. Organism isolated from blood culture

c. Isolation of pathogen from specimen obtained by transtracheal aspirate, bronchial brushing, or biopsy

OR

Criterion 2: Chest radiographic examination shows new or progressive infiltrate, consolidation, cavitation, or pleural effusion AND any of the following:

a. New onset of purulent sputum or change in character of sputum

b. Organism isolated from blood culture

c. Isolation of pathogen from specimen obtained by transtracheal aspirate, bronchial brushing, or biopsy

d. Isolation of virus or detection of viral antigen in respiratory secretions

e. Diagnostic single antibody titer (IgM) or fourfold increase in paired

serum samples (IgG) for pathogen

f. Histopathologic evidence of pneumonia

Together, these outcomes represent the major perioperative pulmonary complications (PPCs). [1]

Independent variables

In order to isolate the impact of intraoperative risk factor on PPCs, both preoperative risk adjustment and intraoperative management variables were collected. Predictor variables studied included those variables identified in prior research as associated with PPCs[10] These include demographics, comorbidities, and surgical procedural risk factors (Data request table attached). In addition, intraoperative management variables were evaluated: total dose of intraoperative vasopressors; use of vasopressor infusions; net fluid intake; number of epochs of absolute and relative hypotension; number of epochs of low pulse oximetry saturation; number of epochs with high tidal volumes, respiratory rates, peak pressures, PEEP, and FIO2; opiate dosing; and use of muscle relaxants and reversal agents (Data request table attached). In addition, patients at risk for perioperative aspiration were identified by documentation of aspiration risk in the anesthesia preoperative history and physical or documentation of rapid sequence induction in the intraoperative record. A rapid sequence induction was defined as a patient administered a rapid onset neuromuscular blockade agent (succinylcholine or rocuronium) with documentation or cricoid pressure or preoperative administration of sodium bicitrate, metoclopramide, or ranitidine, and absence of face mask ventilation attempts.

Data collection Methodology

The data collection methods of NSQIP have been well-described in other papers.[10] Briefly, NSQIP data is collected by a nurse reviewer assigned to each medical center for such collection. The nurse reviewers are trained with respect to the protocol, data-collection methods, patient selection, and variables. Regular communication is maintained to maintain data accuracy and uniformity.[10] A national data analysis center works to coordinate data collection by the nurse reviewers. Periodic site visits are used to assure interrater reliability. During those visits, a nurse reviewer from the chairman's office reviews the case selection, performs an independent reabstraction of a selection of charts, and compares their results with the locally reported results. Site nurses are required to abstract charts within 45 days of the procedure. The data are then submitted to the database after review by the local surgery chief.

Intraoperative AIMS physiologic data is collected using validated, automated interfaces to intraoperative monitor. For continuous variables such as pulse oximetry saturation and invasive blood pressure, values are recorded every 60 seconds. For discontinuous variables such as intermittent non invasive blood pressure, every value is record. Standards of care dictate a blood pressure recorded every three to five minutes. Next, some documentation such as medication administration, is manually entered by the anesthesiology provider during routine clinical care. Structured pick-lists with validation are used to maximize data quality.

Fluid calculation

To normalize fluid administration, crytalloid equivalents will be calculated for each case using the following calculation table. After tabulating the crystalloid fluid equivalent balance for each operation, the resuscitation will be categorized as a **single** categorical variable: *restrictive* (< 6 ml/kg/hr), *standard* (6 to 12 ml/kg/hr), or *liberal* (> 12 ml/kg/hr). The resuscitation category reflects the anesthesiologist's assessment of preoperative fasting deficits, basal fluid requirements, ongoing insensible fluid loss, and third-space fluid loss.

Fluid Balance Additions		
Fluid type	Data element in MPOG database	Conversion Factor to Crystalloid Equivalents
Crystalloid fluid	Total milliliters of crystalloid fluid administered	1:1
Colloid fluid	Total milliliters of colloid fluid administered	2:1
Packed red blood cells	# of units of packed red blood cells administered × 350 ml / unit	3:1
Fresh frozen plasma	# of units of fresh frozen plasma administered × 350 ml / unit	3:1
Platelets	# of units of platelets administered x 50 ml/unit	3:1
Cryoprecipitate	# of units of cryoprecipitate administered x 50 ml/unit	3:1
Fluid Balance Subtractions		
Estimated blood loss	Milliliters of blood loss observed by clinical team	3:1
Urine output	Milliliters of urine output collected by anesthesiologist during operative period	1:1
Other fluid outputs	Ascites drainage, gastric tube drainage, fluid loss	2:1

	from surgical drains	

Statistical Analysis

Statistical analysis was performed using STATA SE version 12 (STATACORP LP., College Station, TX) and RStudio. Descriptive data analysis was used to characterize study population and check for outliers, missing data and the overall integrity of the data. Continuous data were summarized using mean ± SD, or median (inter-quartile range) for skewed distributed data; and discrete data were summarized using proportions. For ease of interpretation age was binned by decade of life with the lowest age group from 18-30, 31-40, etc. In addition, BMI has been categorized based on the World Health Organization (WHO) classifications where normal BMI would be considered the reference group. Pearson's chi-square test, or a two sample t-test/Mann-Whitney was used to check for univariate association between two variables. A p-value of <0.05 was considered statistically significant.

Prior to building any predictive models, all preoperative and demographic variables were assessed for collinearity and bivariate Pearson correlations. Any collinearity that was determined was addressed by either collapsing the variables into one concept or by removing a variable as a covariate prior to placing into a predictive model.

To establish the preoperative baseline risk of a PPC, all demographic and preoperative risk factors (including aspiration risk or rapid sequence induction) were entered into a generalized linear model (GLM) with PPC as the dependent dichotomous outcome variable and the institutional site as a cluster variable. In addition, a composite risk

coefficient for the primary procedure CPT was incorporated (Raval JACS 2010). Independent preoperative predictors of PPC were defined as any predictor with a p-value < 0.05. Adjusted odds ratios and 95% confidence intervals were calculated. This model will result in a single logit score based on the preoperative risk factors and relevant demographic data.

Next, to identify intraoperative predictors of PPC, the patient dataset was divided into four preoperative risk quartiles based upon each patient's logit score derived from the GLM. Within each risk quartile, univariate analysis was performed to assess the association of each intraoperative variable with PPC. Any variables with a univariate trend toward significance were entered into a semi parsimonious logistic regression model with PPC as the dependent dichotomous outcome. Any variables demonstrating significance were defined as intraoperative predictors of PPC.

Power analysis

The current MPOG data including ACS-NSQIP data is approximately 17,000 cases, of which 8,500 are inpatient cases. With an assumed PPC rate of 5%, this should include approximately 425 events. Assuming the need for 10 events per independent variable evaluated, at least 250 events are required to evaluate 25 preoperative variables. Within in preoperative risk class quartile, some low risk quartiles may lack enough events to perform a well-fit regression model.

Limitations

- There may be an insufficient number of events to offer meaningful conclusions for patients in the low risk quartile
- The pathophysiology of respiratory failure and pneumonia may be fundamentally different, and each outcome may need to be modeled separately
- The intraoperative concepts are large in number and reveals the early, exploratory, hypothesis generating nature of the work.
- Manual data entry for fluids and drugs is subject to documentation inaccuracies
- NSQIP patients are a relatively focused group of general and vascular surgery and the conclusions may not apply to other surgery types

Specific data columns required for analysis

Source	***Data Column***	***Data type***	***MPOG Concept***
AIMS (intraop data)	First SBP (invasive or NIBP)	Numeric, 0 – 500	3065, 3030, 3011, 3041, 3046, 3026, 3475, 3015
	First DBP (invasive or NIBP)	Numeric, 0 – 500	3070, 3035, 3012, 3042, 3047, 3027, 3476, 3020
	First MAP (invasive or NIBP)	Numeric, 0 – 500	3075, 3040, 3013, 3043, 3048, 3028, 3477, 3065
	Case length in minutes (patient in room to patient out of room)	Numeric, 0 – 1000	50003, 50008
	# of vasopressor boluses (phenylephrine total /100 mcg + ephedrine total / 5 mg + epinephrine total / 10 mcg)	Numeric	10354, 10355, 10356, 10357, 10358, 10175, 10176
	Vasopressor infusion (phenylephrine, norepinephrine, dopamine)	Yes / no	10354, 10355, 10356, 10357, 10358, 10326, 10165
	Bicitra administration	Yes / no	10130
	Metoclopramide administration	Yes / no	10297
	Ranitidine administration	Yes / no	10387
	Cricoid pressure applied	Yes / no	50116, 50334
	Rapid sequence induction documented	Yes / no	50311
	Total urine output in ML	Numeric, 0 -	10497

		5000	
	Other outputs in ML	Numeric	Aims_intraopinputoutputtotals
	Estimated blood loss in ML	Numeric	10499, 10545
	Total crystalloid in ML	Numeric	Aims_intraopinputoutputtotals
	Total colloid in ML	Numeric	Aims_intraopinputoutputtotals
	PRBCs (units)	Numeric	10489, 10490
	FFP (units)	Numeric	10493
	Platelets (units)	Numeric	10494
	Crystalloid (units)	Numeric	Aims_intraopinputoutputtotals
	# of 10 minute epochs <60 MAP	Numeric, 0 - 100	3075, 3040, 3013, 3043, 3048, 3028, 3477, 3065
	# of 10 minute epochs <50 MAP	Numeric, 0 - 100	3075, 3040, 3013, 3043, 3048, 3028, 3477, 3065
	# of 10 minute epochs <40 MAP	Numeric, 0 - 100	3075, 3040, 3013, 3043, 3048, 3028, 3477, 3065
	# of 10 minute epochs 30% ↓ MAP from baseline	Numeric, 0 - 100	3075, 3040, 3013, 3043, 3048, 3028, 3477, 3065
	# of 10 minute epochs 40% ↓ MAP from baseline	Numeric, 0 - 100	3075, 3040, 3013, 3043, 3048, 3028,

			3477, 3065
	# of 10 minute epochs 50% ↓ MAP from baseline	Numeric, 0 - 100	3075, 3040, 3013, 3043, 3048, 3028, 3477, 3065
	# of 10 minute epochs SPO_2 < 95%	Numeric	3045
	# of 10 minute epochs SPO_2 < 90%	Numeric	3045
	# of 10 minute epochs SPO_2 < 85%	Numeric	3045
	# of 10 minute epochs gas analyzer FIO_2 > 50%	Numeric	3240
	# of 10 minute epochs gas analyzer FIO_2 > 75%	Numeric	3240
	# of 10 minute epochs gas analyzer FIO_2 > 95%	Numeric	3240
	# of 10 minute epochs delivered tidal volume > 10 ml/kg ideal body weight	Numeric	3190, 70259
	# of 10 minute epochs delivered tidal volume > 12 ml/kg ideal body weight	Numeric	3190, 70259
	# of 10 minute epochs delivered tidal volume > 14 ml/kg ideal body weight	Numeric	3190, 70259
	# of 10 minute epochs > 30 measured Peak inspiratory pressure	Numeric	3185
	# of 10 minute epochs > 35 measured Peak inspiratory pressure	Numeric	3185
	# of 10 minute epochs > 40 measured Peak inspiratory pressure	Numeric	3185
	# of 10 minute epochs > 5 measured PEEP	Numeric	70204
	# of 10 minute epochs > 10 measured PEEP	Numeric	70204
	# of 10 minute epochs > 15 measured PEEP	Numeric	70204

	Fentanyl total mcg / weight in kg / surgical duration in hr	Numeric	50003, 50008, 10186
	Morphine total mg/ weight in kg / surgical duration in hr	Numeric	50003, 50008, 10306
	Hydromorphone total mg/ weight in kg / surgical duration in hr	Numeric	50003, 50008, 10219
	Alfentanil total mcg/ weight in kg / surgical duration in hr	Numeric	10020, 50003, 50008
	Sufentanil total mcg/ weight in kg / surgical duration in hr	Numeric	10414, 50003, 50008
	Remifentanil mcg/ weight in kg / surgical duration in hr	Numeric	10390, 50003, 50008
	Succinylcholine administered	Yes / no	10413
	Non-depolarizing neuromuscular blockade administered	Yes / no	10043, 10167, 10305, 10393, 10446, 10344, 10363, 10388
	Last train of four prior to neostigmine dosing	Numeric	10315, 3330, 3485, 3486, 3487, 3488, 3489
	Neostigmine total mg / weight in kg	Numeric	10315
	Naloxone dose mcg	Numeric	10312
	Flumazenil dose mg	Numeric	10191
NSQIP Data	Cardiac, History of CHF	Yes/no	
	Central Nervous System Risk Factors	Character	
	ASA Class	Numeric	
	Drinks >2/day	Yes/no	
	Dependent Functional Status	Yes/no	

	Smoker	Yes/no	
	Pack Years	Numeric	
	Ascites	Yes/no	
	Diabetes	Yes/no	
	Disseminated Cancer	Yes/no	
	Wound infection	Yes/no	
	Steroid use	Yes/no	
	Weight loss > 10%	Yes/no	
	Bleeding disorder	Yes/no	
	Transfusion > 4 U	Yes/no	
	Chemotherapy	Yes/no	
	Radiotherapy	Yes/no	
	Dyspnea (minimal or at rest)	Yes/no	
	History of COPD	Yes/no	
	Acute renal failure	Yes/no	
	On dialysis	Yes/no	
	Emergency	Yes/no	
	Anesthesia Type	Character	
	Inpatient / outpatient	Yes/no	
NSQIP Outcome Variables	30-day mortality	Yes/no	
	On Ventilator > 48 Hours Postop	Yes/no	
	Unplanned Reintubation	Yes/no	
	Postop Pneumonia	Yes/no	

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