Association of anesthesia technique with morbidity and mortality in patients with COVID-19 and surgery for hip fracture: a retrospective population cohort study

Protocol

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Introduction

Background

Patients with hip fracture have poor outcomes (1, 2), attributed to risk factors that include advanced age and higher rates of underlying chronic comorbidities (3). COVID-19 infection is an independent risk factor for increased mortality in hip fracture patients in the perioperative period (4–11). A recent meta-analysis demonstrates COVID-19 infection is associated with higher than seven-fold increase in risk of mortality (12). Recommended management of hip fracture includes timely surgical repair, multimodal pain control, and multidisciplinary follow-up, to facilitate return to mobility and independent function (13, 14).

Anesthesia for hip fracture surgery can be achieved by either general anesthesia (GA) or spinal anesthesia (SA). The potential advantages of SA include opioid-sparing effects, lessened impacts on the respiratory and gastrointestinal systems, and reduction in rates of adverse outcomes such as pneumonia, mechanical ventilation, intensive care unit (ICU) admission, venous thromboembolism (VTE), myocardial infarction (MI), stroke, transfusion, readmission, and prolonged postoperative length of stay (15, 16). However, a recent randomized control trial found no difference between SA and GA for older adults undergoing hip fracture surgery for the primary outcome of survival and recovery of ambulation at 60 days (17).

While emerging evidence shows COVID-19 infection increases mortality after hip surgery, there is a lack of research examining whether the choice of anesthetic technique modifies the postoperative mortality and morbidity of hip fracture patients with COVID-19 infection. This is particularly important due to the high mortality (35% in COVID-positive patients, vs. 2% in patients without COVID) (12), with the potential for SA to modify this risk by circumventing the need for airway interventions. SA may also offer superiority over general anesthesia for limiting aerosol generation and exposure of operating room staff (18) during the pandemic. While SA may reduce the risk of pulmonary morbidity by reducing the need for airway interventions, its motor block on accessory muscles and the need for sedation may adversely impact ventilation.

In this study, our goal is to evaluate the adjusted association between anesthesia technique and mortality and morbidity after hip fracture surgery for patients who tested positive for COVID-19. Our primary objective is to determine for patients undergoing hip surgery with COVID-19 infection, whether SA, as compared to GA, is associated with a lower rate of mortality 30 days postoperatively. Our secondary objective is to determine whether SA, as compared to GA, is associated with a lower rate of morbidity 30 days postoperatively. To provide context for interpretation, we will describe the epidemiology of the following rates during versus before the 2020 COVID-19 pandemic (January to December 2021, compared to 2017 to 2019): 1) SA versus GA utilization for hip fracture surgery, and 2) mortality and morbidity for hip surgery patients without COVID-19 infection. Finally, we will quantify the mortality and morbidity for patients with versus without COVID-19 infection undergoing hip fracture surgery, stratified by SA and GA.

Methods

Study Design

Approval will be gained from the University of British Columbia Providence Health Care Research Ethics Board. The requirement for written informed consent will be waived for use of deidentified data. Patient information will be obtained for the retrospective cohort analysis using the NSQIP® (general dataset linked with the Hip Fracture Procedure Targeted Dataset), a prospectively-collected multicentre dataset with more than 150 clinical variables within 30 days after surgery (19). The study will be pre-registered prior to data analysis (Clinicaltrials.gov) and reported according to The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines.

Setting

The setting of this study will be patient data obtained from the multicentre generated NSQIP Hip Fracture Procedure Targeted Dataset. The period of patient data obtained will include from January 2017 through December 2021. We will omit the data from January 2020 to December 2020 given there was no reporting of COVID status during this period. Data will only be obtained from patients undergoing hip surgery with mortality and morbidity gathered for 30 days postoperatively.

Participants

Inclusion

The study will include all patients 19 years or older who are sampled in the NSQIP Hip Fracture Procedure Targeted Dataset from January 2017 through December 2019 and January to December 2021 undergoing surgical fixation of hip fractures using either general and/or spinal anesthesia. In case of reduced Procedure-Targeted data collection during the COVID-19 pandemic, we will also create a total open hip fracture cohort using relevant *Current Procedural Terminology* codes (27244, 27245, 27269, 27236, or 27248) (20).

Exclusion

Patients with the primary or secondary anesthetic technique listed as local anesthesia alone, local anesthesia with intravenous sedation, epidural, and those with no reported anesthesia technique will be excluded. We will further exclude patients with American Society of Anesthesiologists (ASA) Physical Status (PS) V (defined as "5-Moribund"), and patients with ventilator-dependence preoperatively. Patients with platelet counts $< 80{,}000/mm^3$ within 90 days before surgery (21), INR ≥ 1.5, or PTT > 35 seconds were also excluded for the likelihood of these patients being considered ineligible for SA based on previous guidelines (22, 23).

COVID-19 cohorts

The study will be divided into three cohorts: those undergoing hip surgery 1) without COVID-19 infection January to December 2021, 2) with COVID-19 infection January to December 2021, and 3) pre-pandemic from January 2017 to December 2019.

Due to the variable duration of asymptomatic period that can precede symptoms and diagnosis, COVID-19 infection status will be classified as follows. In our primary analysis, COVID-negative patients will be defined as rows 1 in Table 1, and COVID-positive patients will be defined as row 4. In NSQIP, preoperative COVID status denotes within 14 days before surgery, and patients with preoperative COVID are always coded "No" for postoperative COVID. NSQIP does not have previous history of COVID prior to 14 days, which is a major limitation given the increased mortality of patients with recent COVID undergoing surgery (24).

As patients with postoperative COVID-positive status are difficult to interpret due to variable incubation period and the possibility of COVID-19 contraction while in hospital post-operatively, we will perform sensitivity analysis using alternative definitions for the COVID-positive cohort, including 1) rows 2, 4, and 6 (i.e. laboratory confirmed preoperatively or post-operatively), 2) rows 4 and 6 (i.e. laboratory confirmed or symptomatic preoperatively), and 3) rows 2, 3, 4, 5, and 6 (i.e. suspected and laboratory confirmed anytime preoperatively or post-operatively).

Table 1

Row #	**NSQIP classification**	
	Preoperative COVID (within 14 days before surgery)	**Postoperative COVID**
1	**No**	No
2	No	Yes – lab confirmed
3	No	Yes – suspected
4	**Yes – lab confirmed**	No
5	Yes – suspected*	No
6	Yes – suspected	Yes – lab confirmed

*Suspected denotes COVID-19 infection suspected by patient preoperative pneumonia or dyspnea

Outcomes

All outcomes (please see Appendix 1 for detailed definitions) will be measured within 30 days postoperatively, with the exception of length of stay (LOS) which was the total number of days from the day of operation to the day of discharge from hospital (19).

Primary outcomes

The primary outcome is all-cause 30-day mortality following hip fracture surgery.

Secondary outcomes

Secondary outcomes are MI, stoke or cerebrovascular accident (CVA), postoperative delirium, pneumonia, acute renal failure, transfusion, being on ventilator postoperatively (>48 hours), being still in hospital >30 days, length of stay (LOS), discharge destination as home versus not home, hospital readmission, and unplanned reoperation. There will be three composite outcomes: 1) venous thromboembolism (VTE), defined as pulmonary embolism or deep venous thrombosis, 2) sepsis, defined as sepsis or septic shock, and 3) any complication listed above or death. The definitions of secondary outcomes collected from NSQIP variables are included in Appendix 1 (Data Extraction Form).

Exposure

The exposure to either SA or GA will be modelled as a binary variable (please see Appendix 1 for detailed definitions). SA will be defined as having either spinal or managed anesthesia care (MAC) documented the primary anesthesia technique, without GA secondary anesthesia technique. In NSQIP, regional anesthesia with MAC would be coded as MAC for the principal technique. Since it is highly unlikely that patients can tolerate hip fracture repair under sedation alone, MAC is counted as SA for the analysis. Those receiving both SA and GA (presumably either failed spinal and/or conversion to GA for other purposes) will be excluded from the primary analysis, but included in *a priori* sensitivity analysis with cohort characteristics displayed as a third comparison group, and analyzed as part of the GA group for the multivariable logistic regression.

Confounders

We selected an a *priori* list of potential confounders to adjust for the choice of anesthetic technique, based on availability within NSQIP, literature, clinical experience, and consensus within our multidisciplinary team. The confounders are: age, sex, race, body mass index (BMI) (calculated from height and weight in NSQIP), American Society of Anesthesiologists (ASA) Physical Status (PS), smoker within one year preoperatively, severe obstructive chronic pulmonary disease (COPD), dyspnea, coagulopathy (bleeding disorders), congestive heart failure (CHF), hypertension on medications, preoperative renal failure (acute renal failure, dialysis, and/or GFR < 60 mL/min/1.73 m^2 based on preoperative creatinine) (25), diabetes, preoperative functional status, preoperative delirium or dementia, systemic sepsis, total operating time, and days from hospital admission to operation. The definitions of potential confounding variables collected from NSQIP variables are included in Appendix 1 (Data Extraction Form). Since some of the potential confounders may provide similar information, collinearity will be assessed and variables will be combined or eliminated as described in the statistical analysis plan below.

We acknowledge that NSQIP is missing several important confounders, particularly in terms of having little clinical information indicating the severity of COVID infection, such as the extent of oxygen requirements or admission to higher monitoring settings. In NSQIP, "a patient who is prescribed supplemental oxygen and utilizes it on a regular basis would be assigned as dyspnea upon moderate exertion unless there is documentation of dyspnea at rest".

Statistical Analysis

1. Preprocessing
    1. Convert age from the NSQIP character variable to continuous variable, with Age "90+" recoded as 90
    2. Standardizing the coding of missing values: missing coded in NSQIP as "-99", "unknown", "None Assigned", or "NULL". Each variable will be individually examined to ensure that the missing value is correctly standardized.
    3. Missing values
        - Patients with missing data on key variables will be excluded as described in the inclusion/exclusion criteria.
        - For confounders in modeling, if
            1. >10% missing then exclude the confounder from the model
            2. <1% missing then delete case (complete case analysis)
            3. >=1% and <10% missing then multiple imputation

- The % of missing data for height and weight will be examined in cohort characteristics. If <1% is missing, then BMI will be calculated using these variables.

4. Check for collinearity with variance inflation factor and correlation matrix: if present, combine information from collinear variables if feasible (e.g. new variables is "yes" if "yes" in any of the variables); if not, eliminate the variable that has more missing values or would be less accurately ascertained

2. Descriptive statistics
    1. Cohort characteristics (perioperative and morbidity/mortality outcomes), including by 1) COVID-positive patients by SA vs. GA, 2) COVID-negative patients January-December 2021 vs. 2017-2019, 3) COVID-positive vs. negative in January-December 2021 stratified by anesthesia technique, and 4) utilization of SA vs. GA in 2021 (January-December) vs 2017-2019. Continuous variables will be presented as mean (standard deviation) and median (IQR) for parametric and nonparametric data, respectively. Categorical variables will be presented as frequency (%). For comparison amongst groups, ANOVA will be used for parametric data, Kruskal-Wallis for nonparametric data, and Chi-square for categorical data. Standardized mean difference will be presented.
3. Multivariable logistic regression
    1. To assess the association amongst anesthesia type and mortality in COVID-positive patients, a multivariable logistic regression will be performed using a priori exposure (SA vs. GA) and confounder variables (above) for the primary outcome of mortality. The same independent variables will be used in the multivariable logistic regressions for secondary outcomes (linear regression with log transformation for the outcome of length of stay).
4. Sensitivity and exploratory analysis include
    1. We will define the COVID-positive cohort using the additional definitions discussed above per Table 1.
    2. Cohort characteristics of the GA + SA group will be presented, and compared to the SA and GA groups. If this group consists of >1% of the respective cohort, the multivariable logistic regression for mortality will be repeated with GA+SA included as part of the GA group for the multivariable logistic regression.
    3. Repeat the primary modeling with the cohort after excluding patients with age "90" (all patients aged 90 and above are coded as 90+ in NSQIP, thus potential residual confounding)
    4. If there is sufficient sample size, subgroup analysis by sex (male only, female only) and age (<65, >=65 year old) may be performed.
    5. The degree of unmeasured confounding will be assessed using E-value and the Durbin-Wu-Hausman test.
    6. Adjustment for multiple testing for secondary outcomes, including Bonferroni, False Discovery Rate, and Holm's method
5. Sample size calculation
    1. There are approximately 10,000 patients in the NSQIP Hip fracture dataset per year. The prevalence of COVID-19 in the hip fracture patient population was 10% (thus an estimated sample size of approximately 1000 patients) (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7495188), with a mortality

of 36% in this population. The pre-pandemic SA:GA utilization ratio was approximately 1:4 (20). With 80% power and 0.05 alpha, the sample size required to detect a 10% absolute decrease in mortality rate with the SA exposure (from 36% to 26%) is 1064, and 525 for 14% absolute decrease in mortality rate, as calculated by the Sample Size Calculator (https://clincalc.com/stats/samplesize.aspx).

2. For population cohort studies where logistic regression is used, the sample size recommended is at least 500 patients, or 100 + 50i (i=number of independent variables in the final model) (26). With an estimated sample size of 1000 patients, 18 independent variables can be included.
3. Sample size calculated based on R-squared (variance explained by the multivariable logistic regression) and mortality difference between SA vs. GA (Table 2). Assumptions are: alpha = 0.05, baseline mortality rate 36%, ratio of SA:GA of 1:4. For example, with approximately 500-1000 patients from NSQIP, the study would likely be able to detect a 12 to 14% mortality difference depending on the R-squared.

Table 2. Sample size calculation for logistic regression using G*Power software.

	Detectable difference in mortality			
Amount of R^2 accounted for by covariates	8%	10%	12%	14%
0.1	1820	1139	771	552
0.2	2048	1281	868	621
0.3	2340	1464	992	709
0.4	2730	1708	1157	827

1.

Data will be analyzed using R. Significance level will be set at P <0.05.

List of variables in cohort characteristics include but are not limited to (Please see Appendix 1 for details)

Patient characteristics: Age, sex, race, body mass index (BMI) (calculated from height and weight in NSQIP), American Society of Anesthesiologists (ASA) Physical Status (PS), smoker within one year preoperatively, severe obstructive chronic pulmonary disease (COPD), dyspnea, coagulopathy, congestive heart failure (CHF), hypertension on medications, preoperative renal failure (acute renal failure, dialysis, and/or GFR < 60 mL/min/1.73 m^2 based on preoperative creatinine) (25), diabetes, ascites, preoperative functional status, preoperative dementia/delirium, systemic sepsis, preoperative use of mobility aid, and preoperative pressure sore.

Surgical factors: Total operating time, year of surgery, hip fracture type, pathological fracture, and days from hospital admission to operation.

Systems factors: Medical co-management, and participation in a standardized hip fracture care program.

Postoperative variables:

Mortality
Myocardial infarction
Stroke/CVA
Postoperative delirium
VTE (composite: pulmonary embolism, DVT)
Pneumonia
On ventilator >48h postoperatively
Acute renal failure
Sepsis or septic shock (composite of systemic sepsis and septic shock)
Transfusion (packed red blood cell (PRBC) within the first 72 hours of surgery start time)
Readmission: also present % unplanned
Unplanned reoperation
Still in Hospital > 30 Days
Non-home discharge
Weight bearing as tolerated (WBAT) on postoperative day (POD) #1
Wound issues (composite: superficial and deep infection, wound disruption)
New postoperative pressure sore
Urinary tract infection
Cardiac Arrest Requiring cardiopulmonary resuscitation (CPR)
Postoperative use of mobility aid

Limitations

Due to the retrospective nature of this study, the main limitations include confounding by indication and misclassification. Confounding by indication may be mitigated using multivariable adjustment of potential confounders. Misclassification of COVID is possible due to the limitations of testing and variations in disease presentation.

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