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Development and Internal Validation of a Multivariable Risk Prediction Model for Severe Rebound Pain after Lower Limb Orthopedic Surgery involving Single-Shot Popliteal Sciatic Nerve Blocks: A Single Centre Retrospective Cohort Study

Protocol and Statistical Analysis Plan

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Study Description

Rebound pain is a well-recognized phenomenon after the resolution of peripheral nerve blocks. (1–5) Severe rebound pain is prevalent after ambulatory surgery, with potential resultant increased health-care utilization and cost. (6) Risk factors for severe rebound pain may include younger age, female sex, high preoperative pain score, bone surgeries, and upper limb surgeries. (7–10) Use of tourniquet for lower limb procedures is also associated with worse postoperative pain compared to without. (11,12) Protective factors may include continuous perineural catheter, regional anesthesia adjuncts, and multimodal oral pain management prior to resolution of peripheral nerve blockade. (8,9,13–17) However, placement of continuous peripheral nerve block catheters utilizes additional health care resources; hence, a targeted approach where continuous perineural catheters are offered to patients at the highest risk of severe rebound pain could potentially offer the biggest benefit. The aim of the study is to derive and validate a multivariable prediction model for severe rebound pain after lower limb surgery involving popliteal blockade, to assist with risk stratification and shared decision making.

Primary Objectives

The primary objective of the study is to derive and validate a multivariable clinical prediction model to predict the risk of severe pain after lower limb orthopedic surgeries after single-shot popliteal sciatic nerve blocks resolution.

Data Source

The St. Paul's Hospital Peripheral Nerve Block (PNB) Database (in REDCap) will be used.

Study Sample

Inclusion

Patients undergoing lower limb surgery who received single-shot popliteal sciatic nerve blocks (with or without other peripheral nerve blocks) at St. Paul's Hospital, Vancouver, from January 4, 2016 to November 1, 2019 will be included.

Exclusion

For patients who had multiple surgeries during the study period, only the first surgery within the study period will be selected. Patients who had uncontrolled pain (defined as NRS >3 and/or nursing note documentation of uncontrolled or severe pain and/or undocumented pain status) in the recovery room will also be excluded as this consists of a heterogenous group of patients who may have had failed block or experience pain from sites away from the blocked area, neither of which may be helped by continuous peripheral nerve block catheters. Patients receiving popliteal sciatic nerve catheters will be excluded.

Model Endpoints

The primary endpoint is severe rebound pain, defined by transition from well-controlled pain (numerical rating scale [NRS] 3 or less or patient report of satisfactory pain control) in PACU while the block is working to severe pain (NRS pain score 7 or greater) within 48 h of block

performance. This definition is modified from that of Barry et al., as clinically we have noted some patients having sensory blocks lasting more than 24 hours with the use of adjuncts.

Lower Limb Candidate Predictors

As there is currently no agreed method of classifying lower limb surgeries systematically as it pertains to postoperative pain, we reviewed the literature and consulted an orthopedic surgeon specializing in foot and ankle surgery (Dr. Kevin Wing) to categorize surgeries into a ranked list by anatomy, clinical similarity (e.g. fusion), and known risk factors of increased postoperative acute pain or rebound pain. If multiple surgeries are present, the surgery in the category that is deemed the most involved (i.e. higher ranking) will be selected as the primary surgery.

The following a-priori predictors were included:

- Patient will be assigned one main surgical type (i.e. surgery type is considered one class/categorical variable with Group 9 Soft tissue only as the reference):
  - 1= Fusion/Osteotomy of Ankle/Hindfoot/Midfoot (10,18,19)
  - 2= Total Ankle Replacement (18)
  - 3= Acute Bony Trauma (18–22)
  - 4= Hallux Valgus Surgeries (18)
  - 5= Hardware Removal (18)
  - 6= Amputations
  - 7= Other Ankle/Hindfoot/Midfoot bony procedure (19,23,24)
  - 8= Other Forefoot bony procedure (19,23,24)
  - 9= Soft tissue only (8,18)
- Other surgical predictors
  - Planned admission (Pre- or post-operatively) vs. ambulatory procedure
- Patient characteristics:
  - Age (continuous);
  - Sex (binary);
- Anesthesia-related:
  - Local anesthetic type (Long-acting only vs. mixed);
  - Dexamethasone use (Present or absent);
  - Intraoperative Anesthesia (General anesthesia as defined by need for advanced airway/Sedation/Spinal).

Additional cohort characteristics to be reported:

- Pre-PNB neuropathy (Present or absent; Defined as “Yes” for either Pre-PNB neuropathy or diabetic neuropathy)
- Tourniquet location (Leg versus thigh)
- Tourniquet duration
- Block performer (Attending/ Fellow/ Resident)
- Duration of sensory blockade (as defined by time from PNB performance to return of normal sensation) (Continuous variable);
- Duration of motor blockade (As defined by time from PNB performance to return of normal movement) (Continuous variable);

- Time of day the nerve block wore off (Between 0000- 0700 / Between 0701-2359) (25,26)
- Health care practitioner contact, as defined by answering "yes" to the question of "Did you have to visit the emergency department, or call the surgeon or your family doctor for pain control after your nerve block wore off?".
- Highest pain score (HPS), as defined by the highest NRS pain score upon resolution of peripheral nerve blockade within 48 hours of block performance.

Methods

Data Preprocessing:

Categorization of Lower Limb Surgeries

In the database, the operations performed are entered as free texts, transposed from dictated operative reports. We created a standardized list of keywords and logic protocol to categorize the text variables into groups. Keywords (e.g., "total ankle replacement") will be used to electronically identify main surgical types (e.g., Group 2 = Total Ankle Replacement). Please see Supplementary Material for a full list of keywords and their corresponding surgical types. For patients who fit into multiple surgical types based on keywords, patients will be electronically assigned to the first group on the list. For example, if a patient received both bunionectomy and hardware removal, the patient will be assigned into Group 4= Hallux Valgus Surgery. All surgical assignments will subsequently be manually checked independently by two authors (T.T.H.J. and J.D.), and conflicts will be resolved with a third author (K.W.). To complement this manual check, Cohen's Kappa will be computed to identify the level of agreement of the classifications between the two authors (T.T.H.J. and J.D.), after their respective corrections to the main surgery type classifications.

Missing values

Any variables with >10% missing data among observations will be excluded from the modelling stage. Any variables with <10% missing data among observations will have their missing values imputed using multiple imputation.

Since the primary variable of interest "Main surgery type" has numerous categorical levels, we intend to omit any observations that are missing a "Main surgery type" value, given the greater risk of non-convergence when attempting to impute this variable. Also, any observations with missing values in the primary outcome (rebound pain scores) will be excluded too. The remaining variables are assumed to be missing at random (MAR).

The planned method of multiple imputation will be by using multivariate imputation by chained equations (MICE). The following imputation techniques will be used to impute each variable with missing data:

- "Predictive mean matching" will be used to impute the continuous variables

- Logistic regression will be used to impute the binary variables
- Multinomial logistic regression will be used to impute the nominal categorical variables

All variables (including the outcome) will contribute to imputation of the missing values. The plan of the imputation will be to generate 10 multiply imputed datasets (with an anticipated maximum of 20 iterations to achieve convergence), which will then be used to model and pool results.

Cohort characteristics

Summary statistics of outcomes and candidate predictors will be presented. Continuous variables will be presented as mean (SD) if normally distributed and median (IQR) if not normally distributed, and categorical variables will be presented as frequency (%).

Model building

Correlations amongst candidate predictors will be explored to avoid risks of collinearity (for example, between dexamethasone use and type of intraoperative anesthesia). Amongst multiple highly correlated predictors, only one will be selected for the modeling based on clinical reasoning (e.g. one variable is more easily collected, less missing values, etc.). Additionally, potential multicollinearity within the final model will be diagnosed using variance inflation factors (VIF) of the predictors, with any values exceeding 4 warranting further investigation.

Multivariable logistic regression will be the statistical method used to construct a prediction model, with the above outlined imputation procedure applied to the data prior to modelling. The prediction model will contain the complete variable set as predictors (as outlined in the Candidate Predictors section). “Age”, the only continuous predictor to be included in the model, will be modelled with a natural cubic spline (with 3 interior knots).

In addition, an exploratory prediction model will be created where a natural cubic spline (with 3 interior knots) will also be fitted for an additional predictor of “Tourniquet duration”. This serves as an exploration of whether tourniquet duration plays a predictive role. However, this exploratory model could only be used postoperatively, when this information becomes available. Future database with information on predicted tourniquet duration would be needed for model update to minimize bias if this predictor were to be applied preoperatively. The primary and exploratory models will then be compared in terms of predictive performance and a likelihood ratio test will also be conducted to assess differences in goodness-of-fit.

To assess the performance of the predictive models, we will proceed with a bootstrap validation approach with 100 repetitions. At each repetition, the data will be sampled with replacement to form a bootstrap sample (with sample size equivalent to the original dataset). Multiple imputation will then be conducted on the bootstrap sample prior to modelling (using the same procedure outlined in the above “Missing values” section). After the pooled bootstrap model is created for the given bootstrap sample, performance measures (as discussed below) will be pooled across the 10 multiply imputed datasets of (1) the bootstrap sample and (2) the original

dataset. These will individually form estimates of the "training" and "test" performance, permitting us to compute the optimism of the pooled bootstrap model.

This process will be repeated for each of the repetitions, and optimism estimates will be averaged over the 100 repetitions. Lastly, an estimate of the original model performance will be computed by taking the apparent performance of the original model and subtracting the average optimism.

Model performance measures

To assess model performance, we will use the area under the Receiver Operating Characteristic (ROC) curve (i.e., AUC) and calibration slope to evaluate the discrimination and calibration of the models, respectively. Other overall performance measures that will be computed include the Scaled Brier score and Nagelkerke's R^2. Decile calibration plots will also be generated for the final prediction models to further assess calibration, with Loess-smoothed calibration curves created for each imputed dataset. Additionally, a decision curve analysis will be performed on the final prediction models.

Based on the final validated logistic regression models, a points system will be developed to approximate the contribution of the risk factors in the estimate of risk of having a severe rebound to increase clinical utility of the models. (27)

Sample size
Calculations based on estimated sample size of 1270, and event rate of 50% are shown below. (8) [**https://www.bmj.com/content/368/bmj.m441] (Excel spreadsheet of table below available)**

Binary outcomes		
Figure 1	Margin of error <=0.05	
Criteria iii in pms	Outcome proportion ->	0.5
	Total n needed	384.16
Figure 2	Mean absolute prediction error (MAPE) at 0.05 in predicted probabilities when applied to other targeted individuals	
	number of candidate variables ->	18
	Total n needed	1013.2
Figure 3	Target shrinkage of <=10% (i.e. shrinkage factor = .9), Rsquared CS (proportion of variation explained) at least .1	
Criteria i in pms	Total n needed	716.234
	See Fig 4 for notes: Rsq often .1-.2 for binary for medical; use .5 for direct/explanatory	
Figure 5	n participants required to ensure expected optimisim of <=0.05 in the apparent Rsq	
Criteria ii in pms	Anticipated Rsq	0.2
	Ln L null	-693.15
	Max Rsq (depends on proportion)	0.75

	n Outcome	500
	n total sample size (arbitrary)	1000
	Shrinkage factor corresponding to optimism of <=0.05 in Rsq	0.84211
	Total n needed	420.427

Estimate the overall outcome proportion with sufficient precision (<=0.05)	384.16
Target a small mean absolute prediction error (0.05)	1013.2
Target a shrinkage factor of 0.9	716.234
Target small optimism of 0.05 in the apparent R2Nagelkerke	420.427

Data will be analyzed using R (version 4.0.3). Any statistical tests will be two-sided, with significance levels of 0.05.

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