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Factors associated with rebound pain after peripheral nerve block for ambulatory surgery

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Abstract

Background: Rebound pain is a common, yet under-recognised acute increase in pain severity after a peripheral nerve block (PNB) has receded, typically manifesting within 24 h after the block was performed. This retrospective cohort study investigated the incidence and factors associated with rebound pain in patients who received a PNB for ambulatory surgery.
Methods: Ambulatory surgery patients who received a preoperative PNB between March 2017 and February 2019 were included. Rebound pain was defined as the transition from well-controlled pain (numerical rating scale [NRS] $\leq$3) while the block is working to severe pain (NRS $\geq$7) within 24 h of block performance. Patient, surgical, and anaesthetic factors were analysed for association with rebound pain by univariate, multivariable, and machine learning methods.
Results: Four hundred and eighty-two (49.6%) of 972 included patients experienced rebound pain as per the definition. Multivariable analysis showed that the factors independently associated with rebound pain were younger age (odds ratio [OR] 0.98; 95% confidence interval [CI] 0.97–0.99), female gender (OR 1.52 [1.15–2.02]), surgery involving bone (OR 1.82 [1.38–2.40]), and absence of perioperative i.v. dexamethasone (OR 1.78 [1.12–2.83]). Despite a high incidence of rebound pain, there were high rates of patient satisfaction (83.2%) and return to daily activities (96.5%).
Conclusions: Rebound pain occurred in half of the patients and showed independent associations with age, female gender, bone surgery, and absence of intraoperative use of i.v. dexamethasone. Until further research is available, clinicians should continue to use preventative strategies, especially for patients at higher risk of experiencing rebound pain.

Keywords: ambulatory surgical procedures; dexamethasone; pain management; peripheral nerve block; rebound pain; regional anaesthesia

Editor's key points

- Whilst peripheral nerve blocks (PNBs) can give good analgesia during use, little is known about pain levels after PNBs, nor which patients may be at higher risk or poorly controlled pain.
- Understanding modifiable risk factors can be used to develop targeted strategies and protocols to control rebound pain after PNB.
- This retrospective cohort study found that nearly half of patients experienced severe rebound pain. This was associated with younger age, being female, bone surgery, and no perioperative dexamethasone.
- This study identified intravenous dexamethasone administration as a potentially modifiable independent risk factor associated with a lower incidence of rebound pain, a finding that warrants further investigation.

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An increasing number of orthopaedic and plastic surgeries are conducted in an ambulatory setting under peripheral nerve block (PNB). These types of operations can be associated with severe postoperative pain, especially within the first 24–48 h after surgery.[1] Currently, single-injection PNBs are considered an integral part of multimodal analgesia for postoperative pain that also include acetaminophen, non-steroidal analgesics, and as-needed opioids.[2,3]

PNBs are safe and provide effective analgesia for the initial duration of 6–8 h, contributing to the reduced opioid analgesic requirement and reduced postoperative nausea and vomiting, and expediting hospital discharge.[4]

Surgical pain typically lasts for a variable duration, usually 24–72 h. When PNBs are effective, the pain signals from the surgical site are completely blocked. After resolution of PNB, there may be a relatively rapid increase in the severity of pain. This sudden increase in pain is commonly referred to as 'rebound pain'.[4,5]

Although PNBs lead to improved early pain control and reduced overall opioid use, rebound pain is more likely to

Table 1 Patient characteristics, incidence, and severity (by RPS) of rebound pain after PNB. Differences in total number of patients attributable to missing data. ASA, American Society of Anesthesiologists; AV, arteriovenous; BMI, body mass index; CI, confidence interval; OME, oral morphine equivalent; RPS, rebound pain score; SD, standard deviation.

Total	Total cases, n=993	Rebound pain (%), n=482/972 (49.6)	Mean RPS (95% CI) 6.00
Age (yr) (mean [range])	n=993 (51.4 [13–89])	—	—
BMI (kg m^{-2}) (mean [SD])	n=943 (28.1 [6.06])	—	—
Surgery duration (min) (mean [SD])	n=979 (90.1 [38.0])	—	—
Local anaesthetic volume (ml) (mean [SD])	n=891 (26.4 [11.2])	—	—
Local anaesthetic dose (mg) (mean [SD])	n=891 (147.1 [74.0])	—	—
Sensory block duration (h) (mean [SD])	n=695 (13.1 [9.13])	—	—
Motor block duration (h) (mean [SD])	n=692 (13.1 [11.4])	—	—
Gender	n=972	n=482	—
Male	558	256 (45.9)	5.70 (5.46–5.93)
Female	414	226 (54.6)	6.41 (6.16–6.66)
ASA physcial status	n=786	n=386	—
1	203	103 (50.7)	5.98 (5.61–6.34)
2	470	237 (50.4)	6.01 (5.77–6.25)
3	113	46 (40.7)	5.47 (4.88–6.06)
Surgical site	n=972	n=482	—
Upper limb	838	425 (50.7)	6.07 (5.89–6.26)
Lower limb	123	51 (41.5)	5.40 (4.90–5.89)
Surgical site (specific)	n=961	n=476	—
Hand	568	320 (56.3)	6.50 (6.28–6.71)
Elbow	84	38 (45.2)	5.40 (4.78–6.03)
Shoulder	126	59 (46.8)	5.60 (5.13–6.06)
Knee	84	36 (42.9)	5.40 (4.81–6.00)
Ankle	39	15 (38.5)	5.38 (4.43–6.34)
Vascular (e.g. AV fistula)	60	8 (13.3)	4.00 (3.39–4.61)
Surgery type	n=972	n=482	—
Soft tissue only	474	200 (42.2)	5.47 (5.22–5.73)
Bone surgery	498	282 (56.6)	6.50 (6.28–6.72)
General anaesthesia	n=972	n=482	—
No	738	376 (50.9)	6.15 (5.95–6.34)
Yes	234	106 (45.3)	5.54 (5.19–5.88)
Peripheral nerve block type	n=958	n=476	—
Brachial plexus block	691	351 (50.8)	6.14 (5.93–6.34)
Interscalene block	120	60 (50)	5.87 (5.40–6.33)
Femoral compartment block	90	37 (41.1)	5.38 (4.81–5.95)
Sciatic nerve block	20	8 (40)	5.25 (3.95–6.55)
Distal peripheral neve block	37	20 (54.1)	6.03 (5.14–6.91)
Local anaesthetic drug	n=877	n=428	—
Bupivacaine/Ropivacaine	363	169 (46.6)	5.83 (5.55–6.11)
Surgical mix	443	234 (52.8)	6.25 (6.00–6.49)
Mepivacaine	71	25 (35.2)	5.01 (4.35–5.68)
Analgesia adjuncts	n=972	n=482	—
None	665	348 (52.3)	6.17 (5.96–6.38)
Dexamethasone (mg) (median [range])	169 (6 [4–20])	71 (42)	5.40 (5.01–5.80)
Ketorolac (mg) (median [range])	159 (30 [15–60])	68 (42.8)	5.50 (5.09–5.90)
Opioids in OME (mg) (median [range])	93 (12 [3–48])	41 (44.1)	5.55 (5.00–6.10)
Lidocaine (mg) (median [range])	67 (50 [20–100])	34 (50.7)	5.99 (5.32–6.65)
Ketamine (mg) (median [range])	25 (20 [10–50])	10 (40)	5.20 (4.12–6.28)
Dexmedetomidine (μg) (median [range])	20 (40 [10–100])	9 (45)	6.25 (4.88–7.62)
Postoperative NSAID use	n=421/930	209 (49.6)	6.00 (5.74–6.25)
Postoperative acetaminophen use	n=476/936	220 (46.2)	5.95 (5.70–6.19)
Postoperative opioid use	n=761/952	427 (56.1)	6.40 (6.22–6.59)

manifest between 12 and 24 h postoperatively compared with patients receiving general anaesthesia (GA) alone.[6,7] Rebound pain has been variably described in prior literature. The rebound pain score (RPS) described by Williams and colleagues[8] is a standardised measure of rebound pain severity, calculated as 'the lowest pain score during the first 12 h before the PNB wears off subtracted from the highest pain score during the first 12 h after the PNB wears off". However, a suggested cut-off score to determine the incidence of rebound pain is lacking. This definition requires a pain diary to measure the RPS. A recent review outlined the cardinal features of rebound pain; these include severe pain (numerical rating scale [NRS] $\geq$7 on an 11-point scale), burning or dull in quality, occurring both at rest or on movement, lasting around 2 h, and occurring in the first 12–24 h after the PNB has worn off.[5]

Rebound pain acts as an important limitation of pain resolution and undermines the measures taken to provide adequate analgesia. The experience of rebound pain during the resolution of PNB is contrary to the goal of improving patient satisfaction and reducing persistent pain through adequately controlled pain during the transition from the effects of PNB to oral analgesia. Katz and Seltzer[9] and Katz and colleagues[10] emphasise the importance of such sustained and adequate analgesia in decreasing the chances of persistent pain after surgery.

A number of anaesthetics, surgical, and patient factors have been hypothesised to alter the risk of rebound pain after PNB in prior studies.[5] Some of these factors are risk factors for severe postoperative pain in general, such as age, gender, and presence of preoperative pain.[11,12] Surgery type and site have been previously shown to have an association with rebound pain severity.[8] Some literature has questioned whether local anaesthetics and adjuvants affect perineural inflammation to influence rebound pain.[5,13] Furthermore, block duration and continuous perineural infusion have also been suggested as factors that reduce rebound pain.[5,8]

The primary objective of this study was to identify the incidence and factors associated with an increased incidence of rebound pain in adult patients undergoing ambulatory surgery using PNB. Identifying such factors may enable targeted pain management strategies to specific populations and procedures that are more likely to result in rebound pain.

Methods

This single-centre retrospective cohort study was conducted at Queen Elizabeth II Health Sciences Centre in Halifax, NS, Canada using data from database and questionnaire-based sources. Data collection spanned a 2 yr period between March 2017 and February 2019. Ambulatory surgery was defined as any procedure, where the patient is planned to be discharged directly from the post-recovery unit. PNB was defined as local anaesthetic being deposited at a targeted nerve, whether this was for analgesia primarily or for surgical block (i.e. whether or not the block was combined with GA or sedation). This study is reported in keeping with the Strengthening the Reporting of Observational Studies in Epidemiology guidelines.[14]

Study population

Eligible patients received a PNB by an anaesthetist (or anaesthesia trainee) and were reached for a follow-up telephone call. Queen Elizabeth II Health Sciences Centre is a tertiary care centre where a large number and variety of surgeries are performed using PNBs. All patients who received a PNB were entered into a block room logbook on a daily basis, which identified the ambulatory patients to be included in the study. Patients were excluded if they were inpatients admitted before the day of surgery or were planned to be admitted postoperatively. However, we used an intention-to-treat perspective in that if patients were unexpectedly admitted postoperatively as a result of poor pain control, then they remained in the study.

Patients with a primary block failure were excluded from analysis, defined as patients without a demonstrable sensory block or patients who experienced moderate-to-severe pain (NRS >3) before PACU discharge. Patients who were not reached for follow-up telephone call were called back each day for several days before being noted as 'lost to follow-up' and excluded from the analysis. Ambulatory patients in the block room logbook for a procedure other than a single-shot PNB (i.e. epidural blood patch and spinal anaesthetic) or perineural catheter were also excluded. Patients with any self-reported preoperative opioid use or any residual numbness at time of 24 h follow-up telephone questionnaire were excluded.[15]

Data collection

Local Research Ethics Board (REB) approval was obtained (Reference number 1023603). Data were extracted from hospital databases, the Innovian® intraoperative record system database (Drägerwerk AG & Co., Lübeck, Germany), and the daily telephone follow-up questionnaire. All patients received a follow-up telephone call by the daily block room nurse approximately 24 h after PNB as part of routine care. During this interview, data about the clinically relevant pain and functional outcomes were recorded (Supplementary Appendix 1 shows the questionnaire used for the follow-up telephone call.).

Risk factor variables

Baseline data and potential risk factors were collected (Table 1). Some of these risk factors have been found to be associated with postoperative pain in previous studies.[5,16] Age, gender, BMI, and ASA physical status were included as patient factors. Surgical site and involvement of bone (e.g. bone fusion and internal fixation/pinning) were included as surgical factors. Local anaesthetic type and dose, type of PNB, GA *vs* regional anaesthesia only, and intraoperative co-analgesic medications were included as anaesthetic factors. The use of a 50:50 mixture of ropivacaine (or bupivacaine) with lidocaine to speed up the onset of PNB was called a 'surgical mix'. Type of PNB was grouped as brachial plexus block (axillary, supraclavicular, or infraclavicular block), interscalene block (ISB), femoral compartment block (FCB; femoral nerve block, fascia iliaca compartment block, or adductor canal block), sciatic nerve block (subgluteal and popliteal blocks), and distal PNBs (e.g. ankle and wrist blocks). Pain scores in the PACU and post-discharge use of acetaminophen and NSAIDS were included as postoperative factors. Durations of motor block and sensory block were calculated from block time to when the patients reported motor and sensory resolution of the block, respectively.

Outcome variables

The primary outcome variable for this study was the incidence of rebound pain. Rebound pain is defined as an increase from

well-controlled to severe pain typically within 12–24 h of resolution of the nerve block. No cut-point defining an RPS value at which patients experience rebound pain has been determined, although it has been suggested it must be severe pain (NRS ≥7) after the PNB wears off.[5,8] Thus, the incidence of rebound pain was measured by a change from mild pain (NRS pain score ≤3) when the block was last measured to be working (measured in PACU) to severe pain (NRS pain score ≥7) within 24 h after PNB performance.[17] All patients must have indicated no residual numbness at the 24 h follow-up. The criteria to discharge patients from PACU include adequately controlled pain (NRS ≤3 or patient report of satisfactory pain control). Patients with a transition from moderate pain (NRS 4–6) measured in PACU to severe pain (NRS ≥7) within 24 h of block performance were not considered positive for rebound pain, as moderate pain was not considered to be 'well-controlled' pain. This category of patients may include patients with partial block failure or surgical pain beyond the region covered by a working PNB.

Secondary outcome variables

Secondary outcomes included severity (amplitude) of the RPS, overall patient satisfaction with pain control on a 5-point Likert scale (1=very dissatisfied, 2=dissatisfied, 3=unsure, 4=satisfied, and 5=very satisfied), postoperative readmission or emergency room visit for pain control within 30 days, rate of return to usual activity levels by the time of follow-up telephone call, and whether patients would choose a nerve block again in the future. The RPS by Williams and colleagues[8] was calculated as the difference in NRS pain scores between the lowest pain score in the last 12 h the PNB was working and the highest pain score in the first 12 h after the PNB resolves. We reported a modified RPS as the difference between the last recorded PACU pain score while the PNB was working and the highest pain score reported within the first 24 h after PNB was performed.

Sample size calculation

Two years of data with a total population size of 1800–2000 was expected for analysis based on typical block room throughput at our institution. In this exploratory study, we conducted a sensitivity power analysis for each predictor variable in the multivariate analysis, solving for how large the effect size would need to be in the population for this study to detect it. We also corrected for collinearity (i.e. correlations amongst predictor variables) because collinearity tends to reduce statistical power in multivariable models. Moreover, age and BMI are continuous, whereas other variables are dichotomous. Thus, each parameter in the model required a separate power analysis. Because this analysis was done *post hoc* after viewing the data, some parameters for the power analysis (*N*, collinearity statistics) were drawn from the data set. The variables local anaesthetic type and surgical site were removed after our diagnostics because of small cell sizes.

Power analysis was conducted with G*Power software.[18] This two-tailed test assumed alpha of 0.05, three levels of power (80%, 90%, and 95%), and 49.4% participants with rebound pain of a sample size of 884 (accounting for exclusion criteria and list-wise deletion in multivariable analysis; participants require observations on all variables to be analysed). A standardised (mean=0; standard deviation [SD]=1) normal distribution was assumed for age/BMI, and binomial distributions for other variables. The results of the power analysis are shown in Supplementary Table 2.

Statistical analysis

Patient characteristics data are presented as mean [SD] or number (%) unless otherwise stated. Rebound pain score followed an approximately normal sample distribution; means (95% confidence interval [CI]) were reported for each variable subgroup. Rebound pain score means between patients with and without rebound pain were analysed using Welch's *t*-test (with 5000 bias-corrected and accelerated bootstrapped resamples). Univariate comparisons were analysed by logistic regression for dichotomous outcomes (incidence of rebound pain, return to normal activities, and return to hospital). Linearity of the continuous variables age and BMI with respect to the logit of the dependent variable rebound pain was assessed via the Box–Tidwell (1962) procedure, which demonstrated that both were linearly related to the logit of the rebound pain variable.[19] Univariate linear regression (using 5000 bias-corrected and accelerated bootstrapped resamples) was performed to analyse the association of variables with the RPS secondary outcome.

Multivariable logistic regression was performed for the primary outcome incidence of severe rebound pain. Variables of interest included in the regressions have been studied for association with rebound pain or postoperative pain in previous literature.[5,6,8,16,20] The main model of the primary outcome was developed by identifying variables that are suspected to be associated with rebound pain and clinically relevant confounders chosen *a priori*. The number of variables selected for this model was minimised by removing the least clinically relevant or collinear variables. The Nagelkerke R^2 value and c-index (area under the receiver operating characteristic [ROC] curve) were calculated to assess the ability of the model to explain variations in rebound pain. Postoperative use of prescribed opioids was excluded from all models because of the high likelihood of reverse causation (i.e. patients with more severe rebound pain are more likely to treat it with prescribed opioids).

A *post hoc* machine learning attribute selection method was applied to the full set of putative factors to determine a ranking by association with rebound pain. This served as validation and to determine the relative importance of each putative risk factor. Details of the machine learning methods can be found in the Supplementary methods.

Results

Of 1446 cases identified in the block room logbook, 234 (16.2%) were lost to follow-up. We were unable to match patient identifiers between paper charts and hospital databases for 37 patients, and 15 patients received neuraxial procedures instead of a PNB. Of the remaining cohort, patients were excluded based on preoperative opioid use (*N*=23), receiving a continuous perineural catheter (*N*=14), having moderate-to-severe pain (NRS >3) as their last recorded pain score in PACU (*N*=85), or reporting residual numbness at the time of 24 h follow-up questionnaire (*N*=45). Nine hundred and ninety-three patients remained in the sample cohort after inclusion and exclusion criteria (Fig. 1). Patient characteristics features and incidence and severity of rebound pain within

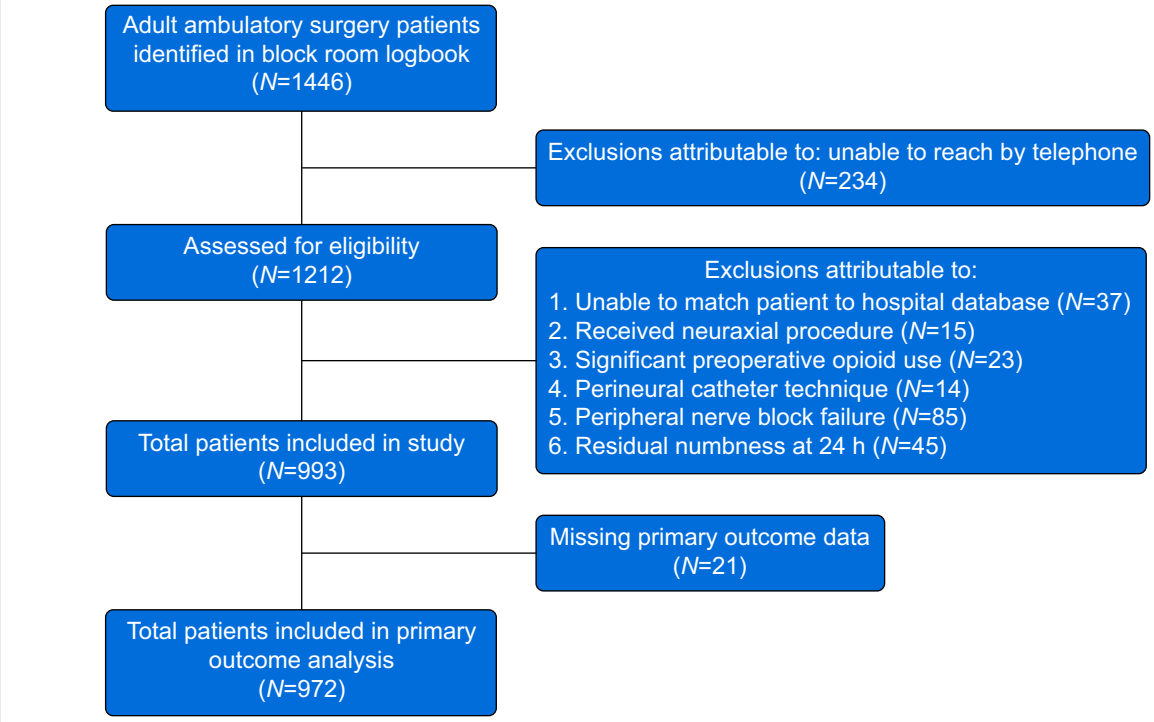

Fig 1. Study flow chart.

factors are shown in Table 1. Amongst the cohort, 972 reported a maximum pain score after discharge; 482 (49.6%) of these patients experienced rebound pain, defined as experiencing severe postoperative pain at home after discharge when the last PACU pain was mild. The overall mean RPS was 6.0. Those classified as without rebound pain had a mean RPS of 3.80 [1.78], whereas those classified with rebound pain had a mean RPS of 8.24 [1.30], respectively, with a mean difference 4.45 (95% CI 4.26–4.65; $P<0.001$).

Postoperative analgesics were prescribed by the surgical team and were highly variable by dose and frequency, given the retrospective nature of this study. Postoperative oral NSAID use most commonly included ibuprofen (82.1%), with the remaining patients reporting use of naproxen, diclofenac, ketorolac, and celecoxib. Postoperative opioid prescription most commonly included oral hydromorphone (71.3%), with the remaining patients reporting use of codeine, oxycodone, tramadol, morphine, and meperidine.

Statistically significant factors associated with a higher risk of rebound pain on univariate analysis were younger age, female gender, bone surgery, and postoperative opioid use (Table 2). Intraoperative i.v. dexamethasone was associated with a lower risk of rebound pain. Similarly, with respect to RPS, female gender, bone surgery, upper limb surgery, and brachial plexus blocks were associated with a higher RPS (Supplementary Table 1). Femoral compartment block, GA, and intraoperative use of i.v. dexamethasone and ketorolac were associated with a lower RPS. There was strong collinearity between femoral block, lower limb surgery, and GA. There were low rates of dexamethasone and ketorolac usage in patients without GA (4.2% and 6.2%, respectively) compared with GA (58.4% and 47.9%, respectively). Although i.v. dexamethasone appeared to be associated with a longer duration of sensory block (mean 17.6 [8.10] h) compared with the absence of dexamethasone (mean 12.1 [9.06] h) with a mean difference of 5.48 h (95% CI 3.91–7.09 h; Welch's t-test P-value <0.001), this did not remain significant in a bootstrapped linear regression when including covariates with potential for confounding, such as GA, i.v. ketorolac, local anaesthetic drug type and volume administered, and PNB block type (P-value=0.416). Duration of sensory block was not found to be associated with the incidence of rebound pain (P-value=0.625) nor RPS (P-value=0.685) in regression analysis.

Seven variables were included in a multivariable analysis based on prior literature on predictors for severe postoperative pain and persistent post-surgical pain (Fig. 2). Confounders, such as GA and BMI, were included, given that GA may be an indicator of an incomplete block and BMI has been associated with worse postoperative pain.[21,22] The surgical site was selected for inclusion in the model *a priori*, but was found to be highly collinear with GA, and thus was left out of the main model. Intraoperative opioid, ketamine, lidocaine, and dexmedetomidine were excluded from the model, as patients receiving them received GA almost exclusively. Of factors not reaching statistical significance (BMI, GA, and home NSAIDs), none had odds ratios (ORs) beyond the effect size cut-offs at 80%, 90%, or 95% power determined by the sensitivity power analysis (Supplementary Table 2). Any association between these factors and rebound pain cannot be reliably detected, and thus is inconclusive with the sample size.

When excluding surgical site, factors that were independently associated with a higher incidence of rebound pain on

Table 2 Univariate logistic regression analysis of putative factors for association with incidence of rebound pain. ASA, American Society of Anesthesiologists; CI, confidence interval; OME, oral morphine equivalent; OR, odds ratio. *Age (per decade): OR 0.877 (95% CI 0.817–0.942).

Variable	Reference group	OR	95% CI	P-value
Age (per year)*	—	0.987	0.980–0.994	<0.001
BMI	—	0.991	0.970–1.013	0.426
Gender	Male	1.418	1.099–1.831	0.007
Surgery type (bone)	Soft tissue	1.789	1.387–2.306	<0.001
No general anaesthesia	General anaesthesia	1.254	0.934–1.685	0.132
Dexamethasone (absence)	Dose range 4–20 mg i.v.	1.447	1.035–2.024	0.031
Postoperative NSAID use	No NSAID use	1.005	0.777–1.302	0.967
ASA physical status				
2	1	0.988	0.710–1.373	0.941
3		0.667	0.419–1.062	0.088
Surgery duration (min)	—	1.000	0.997–1.004	0.821
Surgical site (upper limb)	Lower limb	1.453	0.990–2.132	0.056
Peripheral nerve block type				
Interscalene block	Brachial plexus block	0.969	0.657–1.427	0.872
Femoral compartment block		0.676	0.433–1.056	0.085
Sciatic nerve block		0.646	0.261–1.599	0.345
Distal peripheral nerve block		1.140	0.587–2.213	0.699
Local anaesthetic drug				
Surgical mix	Bupivacaine/ropivacaine only	1.285	0.973–1.697	0.077
Mepivacaine		0.624	0.368–1.059	0.080
Local anaesthetic volume (ml)	—	1.007	0.994–1.019	0.310
Local anaesthetic dose (mg)	—	0.998	0.996–1.000	0.052
Sensory block duration		0.996	0.980–1.012	0.625
Motor block duration		0.988	0.974–1.003	0.109
Ketorolac	No ketorolac	0.720	0.511–1.015	0.061
Ketamine	No ketamine	0.671	0.298–1.508	0.334
Lidocaine	No lidocaine	1.051	0.640–1.727	0.844
Dexmedetomidine	No dexmedetomidine	0.829	0.340–2.018	0.697
Intraoperative opioid (in OME)	No intraoperative opioid	0.783	0.509–1.204	0.265
Postoperative acetaminophen use	No acetaminophen use	0.802	0.620–1.036	0.091
Postoperative opioid use	No opioid use	3.705	2.598–5.283	<0.001

multivariable logistic regression were younger age, female gender, bone surgery, and absence of i.v. dexamethasone (Fig. 2). The model achieved a significant χ^2 test with $P<0.001$ and Nagelkerke R^2 of 0.078. The c-statistic (the area under the ROC curve) for the model was 0.639 (95% CI 0.603–0.675; see Supplementary Fig. 1). A second model was run replacing the variable GA with the surgical site; upper limb site was found to be significantly associated with rebound pain, suggesting that upper limb site could be an independent predictor. On further exploratory analysis, upper limb surgery only trended towards significance when the surgical site was introduced into the multivariable model, including GA (adjusted OR 1.544; 95% CI 0.958–2.489; $P=0.075$) with an R^2 of 0.083 and c-statistic of 0.644 (95% CI 0.608–0.680) (Supplementary Table 3).

A machine learning algorithm called 'logistic model tree attribute-selected classifier' yielded the highest performance of all tested algorithms in predicting rebound pain from all putative variables, with an area under the ROC curve of 0.609. A ranked list of risk factor variables was produced based on their average correlation ('merit' in machine learning terms) with rebound pain. The top factors in order of decreasing merit were bone surgery, gender, local anaesthetic drug type, age, motor duration, and i.v. dexamethasone (Fig. 3). Bone surgery reached the highest merit by a significant margin above the rest, indicating this may be most important in the development of rebound pain. This method identified two factors not included in the multivariate logistic regression model: local anaesthetic drug type and motor block duration. This finding warrants further investigation into their potential impact on rebound pain.

In this study, 81.9% patients experienced moderate-to-severe pain (NRS ≥4), and 49.6% experienced severe pain (NRS ≥7) at some time between their PACU stay to follow-up telephone call questionnaire (Table 3). Despite a high rate of rebound pain, 83.2% of patients reported they were 'satisfied' to 'very satisfied' with their overall pain control. For every 1 point increase in the RPS, patients were anywhere from 1.7 to 2.4 times more likely to express dissatisfaction with their pain management (OR 2.040; 95% CI 1.731–2.403; $P<0.001$). Only 3.5% of patients were unable to return to usual daily activities by time of follow-up telephone call and 4.4% returned to care to receive treatment for intolerable pain, both of which were significantly associated with the RPS. Ninety-six percent of patients reported that they would choose a nerve block again for future surgery.

Discussion

This retrospective study identified severe rebound pain in around half of the ambulatory surgery patients included. A large difference in the RPS was found between patients with and without rebound pain, suggesting this may be a useful measure of the incidence of rebound pain in the ambulatory surgery population. In the primary multivariate analysis, this

Variable	Reference category	OR	95% CI	*P*-value
Age (per year)	—	0.980	0.972–0.988	<0.001
Age (per decade)*	—	0.817	0.753–0.886	<0.001
BMI (per kg m^{-2})	—	0.997	0.975–1.020	0.811
Gender (female)	Male	1.520	1.146–2.015	0.004
Bone surgery	Soft tissue	1.823	1.384–2.402	<0.001
General anaesthesia	No GA	1.272	0.845–1.914	0.250
Dexamethasone (absence)	Dexamethasone	1.784	1.123–2.833	0.014
Postoperative NSAID use	No postoperative NSAID	0.947	0.717–1.250	0.700

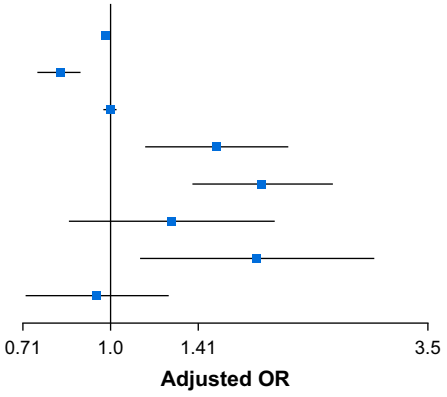

Fig 2. Forest plot of factors analysed for association with incidence of rebound pain in multivariable logistic regression (error bars represent 95% confidence interval [CI]; N=884/972 after missing data points excluded). *Age (per decade) values for odds ratio (OR) and 95% CI represent derived values from age (per year). GA, general anaesthesia.

study identified three non-modifiable patient and surgical risk factors for rebound pain: younger age, female gender, and bone surgery. Surgical site, local anaesthetic type, and absence of ketorolac use showed a trend towards association with rebound pain. Of the anaesthetic factors, i.v. dexamethasone administration was the only modifiable factor that may be associated with a reduction in rebound pain. Patient satisfaction was high despite the high rate of rebound pain, possibly suggesting it was a minor or brief aspect of patients' overall perioperative experience. Furthermore, there was a much lower rate of patients returning to care for pain control compared with the literature reported values of up to 20% of patients for ambulatory wrist-fracture surgery via regional anaesthesia.[23]

Our primary outcome captures rebound pain that occurs within 12–24 h of block resolution and severe pain after ambulatory patient discharge, which is a significant patient-centred morbidity outcome.[24] The original RPS utilising patient pain diaries undoubtedly provides a rich measure of the severity, timing, and duration of rebound pain; however, it may not be as practical in institutions with high volume. The RPS used in this study is consistent with the timing described by Williams and colleagues,[8] which calculated the RPS from pain scores in the first 12 h after block resolution. With an average sensory block duration of 13.1 [9.13] h, pain scores acquired at 24 h from the time the block was performed would capture the majority of rebound pain arising within the first 12 h after block resolution. Using this approach to capture the incidence of rebound pain, it is therefore possible that late-onset rebound pain occurring after 24 h from the time of PNB performance could be missed. A previous study defined an NRS pain score of 3.3 or less as the patient acceptable symptom state after surgery, which is the 'value beyond which patients consider themselves well'.[25] Based on this, patients with moderate-to-severe pain (NRS >3) before PACU discharge were deemed to have poorly controlled pain in PACU. This could have been attributable to block failure, early/partial block resolution, or pain from surgical areas outside the area covered by the block. These patients were excluded, as rebound pain should be the transition from adequately controlled pain before discharge to severe pain when the patient is at home.

The mean RPS of 6.00 in this study represents the increase in pain felt after a large variety of surgical procedures and regional anaesthetic techniques; however, 86.2% of patients underwent upper limb surgery and 58.7% received hand surgery in particular. The mean RPS value found in this cohort is consistent with previous reports of postoperative pain scores at 12–24 h after hand surgery.[26,27] McCartney and colleagues[27] found that patients had mean VAS pain scores of approximately 60 out of 100 points on postoperative Day 1 after a variety of similar hand surgeries to those in the present study (e.g. tendon and nerve repair, fracture open reduction internal fixation, arthrodesis, and hardware removal/revisions). Prior studies of pain after brachial plexus block for distal radius fracture repair and ISB for arthroscopic rotator cuff repairs have shown increases of 4–5 VAS points between Hour 1–2 and Hour 12 postoperatively.[6,28] Lower limb surgery was associated with lower RPS scores similar to the study by Williams and colleagues[8] that reported a mean RPS of 2.0 for FCB in anterior cruciate ligament reconstruction. Ambulatory knee surgery is typically performed with the combination of femoral nerve compartment block combined with GA as a result of knee innervation by multiple nerves of the lumbar plexus and the sciatic nerve. As the knee is only partially supplied by the femoral nerve, the increase in pain (the RPS) after an FCB wears off may be less than for regions completely covered by a PNB. Also, minimally invasive arthroscopic techniques to repair soft tissue structures of the knee may explain the lower severity of postoperative pain. This is in contrast to upper limb procedures (with the exception of shoulder surgery), where patients are less likely to require GA, as brachial plexus block provides a complete block of all nerves supplying the upper limb. If such patients have not started adequate oral analgesia before the block resolution, they may experience a large, sudden increase in pain when the block wears off. Upper limb surgery patients are also less likely to be given co-analgesic medications, such as i.v. dexamethasone and ketorolac, which would be routine during GA.

Dexamethasone has been shown to prolong PNB duration when given perineurally compared with intravenously,

Table 3 Secondary outcomes of maximal pain severity, patient satisfaction with pain control, return to hospital for uncontrolled pain, return to daily activities, and whether patient would choose a PNB again. CI, confidence interval; NRS, numerical rating scale; OR, odds ratio; PNB, peripheral nerve block.

		Mean RPS (95% CI)	OR (95% CI)	P-value
Pain severity group	Total N=972 (%)			
Mild (NRS 0–3)	176 (18.1)	1.91 (1.74–2.08)		
Moderate (NRS 4–6)	314 (32.3)	4.85 (4.74–4.97)		
Severe (NRS 7–10)	482 (49.6)	8.24 (8.13–8.36)		
Satisfaction	Total N=981 (%)			
Very dissatisfied	22 (2.2)	8.95 (8.15–9.76)	2.040 (1.731–2.403)	<0.001
Dissatisfied	61 (6.2)	8.80 (8.39–9.20)		
Neutral	82 (8.4)	7.52 (7.02–8.03)	Reference	
Satisfied	558 (56.9)	6.00 (5.80–6.20)		
Very satisfied	258 (26.3)	4.56 (4.21–4.92)		
Return to care/hospital	Total N=962 (%)			
Yes	42 (4.4)	7.93 (7.15–8.71)	1.416 (1.216–1.648)	<0.001
No	920 (95.6)	5.91 (5.74–6.09)	Reference	
Return to daily activities	Total N=977 (%)			
Yes	943 (96.5)	5.96 (5.78–6.13)	0.882 (0.769–1.010)	0.070
No	34 (3.5)	6.82 (5.92–7.73)	Reference	
Would choose PNB again	Total N=958 (%)			
Yes	923 (96.3)	5.92 (5.74–6.10)	0.873 (0.763–0.998)	0.047
No	35 (3.7)	6.86 (5.92–7.79)	Reference	

although a recent systematic review showed that either route is equivalent in terms of duration of block analgesia, 24 h pain scores, and cumulative opioid consumption at 24 h postoperatively.[29,30] There was no independent effect of dexamethasone on block duration in the current study, although it was associated with a reduced RPS and incidence of rebound pain. Furthermore, to our knowledge, dexamethasone given through any route has not specifically been studied for association with rebound pain after PNB. I.V. dexamethasone at single doses greater than 0.1 mg kg^{-1} has been shown to reduce postoperative pain in a prior meta-analysis.[31] The reduction in rebound pain incidence and RPS found may be consistent with the known effect of i.v. dexamethasone on postoperative pain in general rather than any possible effect on PNB duration. Further prospective research elucidating the beneficial effects of i.v. dexamethasone on reducing rebound pain is warranted based on this study.

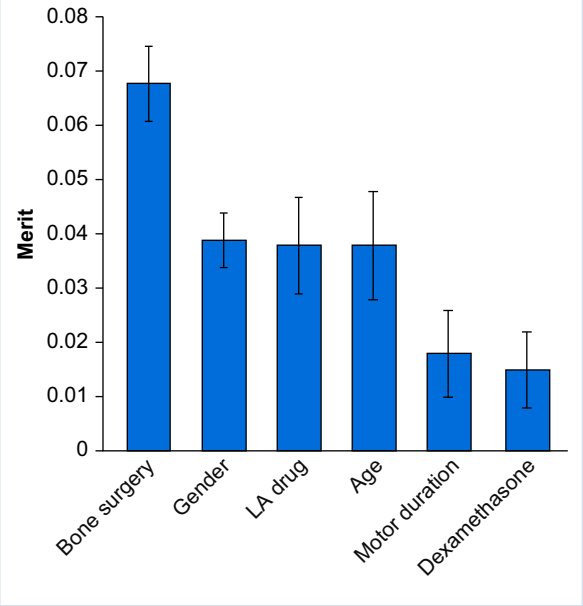

Fig 3. Average merit of top predictive risk factor variables identified using logistic model tree algorithm in 972 patients using Weka 3.9.3 machine learning software. Merit is the individual contribution of each variable added to the overall correlation with the outcome of rebound pain. Error bars represent standard deviation. LA, local anaesthetic.

Preoperative pain level had been shown to be a significant predictor of severe postoperative pain in a number of studies across a variety of noncardiac ambulatory surgery types, a variable not collected for this study.[11,12,32,33] Other weaknesses of this study include the retrospective nature of the database, reliance on patient memory to record some of the putative risk factors, and potential for numerous confounders present. Unfortunately, although sensory testing of PNBs is routine before incision, documentation specifying PNB failure as the reason for GA is lacking in this study. In addition, compliance with the postoperative use of NSAIDs and acetaminophen was unknown, and documentation of the dose and timing of these medications was highly variable. Another limitation was the exclusion of opioid-tolerant patients and continuous PNB catheters in the database, factors which may presumably have a significant impact on the development of rebound pain. There were also no perineural adjuvants used in any patients in this study. A particular strength of this study is its large cohort size and the diversity of factors studied for association with rebound pain, potentially representing the largest single investigation on rebound pain to date. With the increasing integration of machine learning into biomedical research, this study also benefits from incorporating a machine learning approach to clarify the relative importance of factors associated with rebound pain.

Future studies on rebound pain should include a preoperative pain score recorded before PNB, the specific timing of maximal rebound pain after hospital discharge, and

documentation of PNB failure if and when it was the indication for GA. Prospective studies on the use of continuous PNB catheters, the effect of PNB adjuvants or co-analgesic medications (e.g. i.v. dexamethasone), and timing of postoperative oral analgesia would be beneficial to determine the most effective preventive strategies.

In conclusion, this retrospective study of 972 ambulatory surgery patients that received a PNB showed a relatively high incidence of rebound pain across a large variety of surgical procedures. Factors associated with an increased risk of rebound pain were younger age, female gender, surgical procedures involving bone, and the absence of perioperative i.v. dexamethasone use. Other factors with a trend towards association were surgical site, local anaesthetic type, and absence of ketorolac use. Despite a high incidence of rebound pain, the vast majority of patients were satisfied with their pain management, did not require a return to care for pain control, and returned to their usual daily activities by the time they were followed-up.

Authors' contributions

Study conception: VU
Study design: JGB, VU
Research proposal: GSB, VU
Grant funding applications: GSB, JGB, VU
Research Ethics Board (REB) application: GSB, VU
Research Ethics Board (REB) maintenance: GSB
Data collection: JS, PB
Database construction: PB
Database management: GSB, PB, JS
Data cleaning/pre-processing: GSB
Statistical analysis: GSB, JGB, VU
Writing of paper: GSB, VU
Editing of paper: JGB, JS

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George Campanis (senior systems analyst) significantly contributed to the data collection and database construction from existing hospital electronic databases and with expert consultation for the machine learning methods undertaken. Sean P. Mackinnon (statistician) contributed to the statistical power analysis and expert consultation on statistical methods, such as univariate and multivariate analyses. Kwesi Kwofie and Vishal Uppal were instrumental in establishing the format and routine documentation of the follow-up telephone call questionnaire after peripheral nerve block at the Queen Elizabeth II Health Sciences Centre, Halifax, NS, Canada.

Declarations of interest

The authors declare that they have no conflicts of interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bja.2020.10.035.

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