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ORIGINAL ARTICLE

Cigarette smoking, opioid consumption, and pain intensity after major surgery: An observational study

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Abstract

Background: Chronic exposure to nicotine may change pain perception and promote opioid intake. This study aimed to evaluate the putative effect of cigarette smoking on opioid requirements and pain intensity after surgery.

Methods: Patients who underwent major surgery and received intravenous patient-controlled analgesia (IV-PCA) at a medical center between January 2020 and March 2022 were enrolled. Patients' preoperative smoking status was assessed using a questionnaire by certified nurse anesthetists. The primary outcome was postoperative opioid consumption within 3 days after surgery. The secondary outcome was the mean daily maximum pain score, assessed using a self-report 11-point numeric rating scale, and the number of IV-PCA infusion requests within three postoperative days. Multivariable linear regression models were used to calculate the regression coefficient (beta) and 95% confidence interval (CI) for the association between smoking status and outcomes of interest.

Results: A total of 1162 consecutive patients were categorized into never smokers (n = 968), former smokers (n = 45), and current smokers (n = 149). Current smoking was significantly associated with greater postoperative opioid consumption (beta: 0.296; 95% CI, 0.068-0.523), higher pain scores (beta: 0.087; 95% CI, 0.009-0.166), and more infusion requests (beta: 0.391; 95% CI, 0.073-0.710) compared with never smokers. In a dose-dependent manner, smoking quantity (cigarette per day) was positively correlated with both intraoperative (Spearman's rho: 0.2207, $p = 0.007$) and postoperative opioid consumption (Spearman's rho: 0.1745, $p = 0.033$) among current smokers.

Conclusion: Current cigarette smokers experienced higher acute pain, had more IV-PCA infusion requests, and consumed more opioids after surgery. Multimodal analgesia with nonopioid analgesics and opioid-sparing techniques, along with smoking cessation should be considered for this population.

Keywords: Narcotic; Nicotine; Pain sensitivity; Postoperative pain

1. INTRODUCTION

Adequate pain control is essential for surgical patients. Epidemiological studies have shown that up to 80% of patients in the United States had inadequate control and management for acute postoperative pain.[1] Poorly controlled postoperative pain is associated with postoperative complications, functional and quality-of-life impairment, and potential transition into persistent or chronic pain.[2,3] Opioids are commonly used to relieve moderate to severe pain after surgery.[4] Multiple variables affect postoperative opioid consumption, including patient-related (eg, age, sex, and depressive or anxiety disorders), surgery-related (eg, surgical sites and use of minimally invasive techniques), and anesthesia-related factors (eg, anesthesia modalities and nonopioid analgesia techniques).[5–7]

Smoking is a leading preventable cause of disease and premature death worldwide.[8] For surgical patients, active smoking may increase the risk of perioperative pulmonary complications and mortality.[9] Chronic exposure to nicotine and cigarette smoke may cause desensitization of nicotine acetylcholine receptors (nAChR) and could change pain perception in humans.[10] Furthermore, accumulating evidence has indicated that cigarette smoking may influence narcotic requirement, pain severity, and the risk of chronic pain after surgery.[11–22] However, the association between smoking and opioid consumption or pain intensity is not clear due to conflicting results, with positive associations reported in some studies[11–14,16–20,22] but not in others.[15,21] In

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addition, some methodological drawbacks reduced the validity of previous studies, including small sample size (n < 1000),[11,14,17–22] inadequate control for confounding factors,[11,19,22] and restriction to specific types of surgery.[11,12,15–19,21,22] Importantly, some preceding studies only evaluated postoperative opioid consumption[11,15,21] or pain severity,[12] which limited the interpretation of the study results.

We conducted a single-center, retrospective, cohort study to investigate the association between cigarette smoking and postoperative opioid consumption, pain intensity, or opioid seeking behaviors. This study also examined the potential dose-dependent relationship between smoking quantity, smoking duration, and postoperative pain outcomes. Based on the current evidence,[11–22] we hypothesized that current cigarette smoking was associated with greater opioid consumption, higher pain intensity, and more opioid requests after major surgery.

2. METHODS

2.1. Patient selection criteria

This study was reviewed and approved by the Institutional Review Board of Taipei Medical University, Taipei, Taiwan (approval number: TMU-JIRB-N202205095). The Institutional Review Board waived the need for written informed consent due to the retrospective nature of this study. All methods were performed in accordance with the Declaration of Helsinki 2013 and study guidelines.[23] We reviewed the electronic medical records of patients who underwent major surgery requiring postoperative hospitalization for ≥2 days, who received general or regional anesthesia, and who used intravenous patient-controlled analgesia (IV-PCA) for postoperative pain control at a medical center in Taipei, Taiwan between January 2020 and March 2022. This study included patients using IV-PCA to minimize heterogeneity in postoperative pain management and to accurately quantify opioid consumption. Exclusion criteria were missing data about postoperative opioid dosage, duplicate cases, age <18 years, the use of IV-PCA for <48 hours, inability to report pain severity, and postoperative pain assessments for <2 days.

2.2. Smoking status before surgery

The patients' smoking status was assessed using an online self-reported questionnaire which was administered by certified nurse anesthetists 1 day before surgery. The questionnaire data were validated using the medical records of previous hospital admissions. Patients were classified into never or ever (former or current) cigarette smokers. Ever smokers were defined as those patients who had smoked ≥100 cigarettes while never smokers were defined as those who had smoked <100 cigarettes throughout their lifetime.[24] Among the ever smokers, subjects who had smoked within the 30 days before the index surgery were classified as current smokers; otherwise, subjects were classified as former smokers.[24] For current smokers, we also evaluated smoking quantity (number of cigarettes smoked per day) within the past 30 days and smoking duration (years). Active smokers were advised to stop smoking at least 24 hours before surgery and were not provided with any nicotine replacement therapy before or during their hospital admission.

2.3. Postoperative analgesia protocol

After surgery, patients were transferred to the postanesthesia care unit where IV-PCA was initiated. Contraindications to IV-PCA included no reasonable level of consciousness or cognitive function and the need for postoperative mechanical ventilation or intensive care for >24 hours. A PCA infusion pump (CADD®-Solis Infusion System, Smiths Medical, Inc., Minneapolis, MN, USA) was used to intravenously deliver morphine sulfate 1 mg·mL^{-1} in normal saline, as reported in our previous studies.[5,25,26] Fentanyl 10 μg·mL^{-1} was used for patients with advanced chronic kidney disease (estimated glomerular filtration rate <30 mL·min·1.73 m^{-2}) or impaired liver function. Our pain service team educated the patients on using the PCA pump correctly before and after surgery. A loading dose of morphine 0 to 0.1 mg·kg^{-1} or fentanyl 0 to 1 μg·kg^{-1} was used for immediate pain control upon arrival at the postanesthesia care unit. PCA pumps were set to deliver a demand dose of 0.5 to 2.0 mL, with a continuous basal infusion rate of 0 to 1.5 mL·h^{-1}, and had a lockout interval of 5 to 10 minutes. IV-PCA was typically used for 48 to 72 hours after surgery. The pain service team measured opioid consumption and determined pain intensity at 12-hour intervals. The IV-PCA infusion parameters were adjusted if patients had inadequate pain relief or opioid-related adverse effects (eg, nausea, vomiting, and dizziness). Single or repeated intravenous boluses of ketorolac 15 to 30 mg were given in case of inadequate analgesia after IV-PCA dose adjustments.

2.4. Study outcomes

The primary outcome was postoperative opioid consumption within 3 days after surgery. The total opioid dosage of IV-PCA for each patient was acquired from the PCA pump machine. The dosages of opioids other than morphine were transformed into morphine milligram equivalents (MMEs) for further analyses (Supplementary Table S1, http://links.lww.com/JCMA/A189).[27,28]

The secondary outcome was the mean daily maximum pain score within three postoperative days. Postoperative acute pain was assessed both at rest and during movement using a self-report 11-point numeric rating scale (NRS) with response options from "no pain" (0) to "the worst pain" (10); this was administered by certified nurse anesthetists at 12-hour intervals for 3 days after surgery. We also assessed the number of infusion requests and injection denials on the IV-PCA within three postoperative days to investigate the potential influence of cigarette smoking on opioid seeking behavior.

2.5. Patient and clinical covariates

Collected covariates included age, sex, body mass index, American Society of Anesthesiologists physical status, current alcohol drinking, and sedative-hypnotic use within 30 days before surgery. Surgical variables included surgical sites, uses of laparoscopic or robotic techniques, and intraoperative blood loss. Anesthetic variables were type of anesthesia, anesthesia duration, dosage of intraoperative dexamethasone, peripheral nerve blockade, and intraoperative opioid consumption. Coexisting diseases included hypertension, diabetes mellitus, depression disorder, and cancers. Laboratory tests measured preoperative serum levels of hemoglobin, creatinine, aspartate aminotransferase and alanine aminotransferase, and estimated glomerular filtration rate (based on the Cockcroft-Gault formula).[29] All data were extracted by a medical physician who was not involved in the data analysis. Random samples of the extracted data were thoroughly checked and audited by other investigators to ensure data quality.

2.6. Statistical analysis

The Shapiro-Wilk test and Kolmogorov-Smirnov test were used to check the normality of the included variables. Normally distributed variables were presented as the mean ± standard deviation. Non-normally distributed data were expressed as the median and interquartile range (IQR). Logarithmic transformation with base 2 was used to decrease the skewness of non-normal continuous variables, including postoperative and intraoperative opioid consumption, postoperative pain scores,

numbers of IV-PCA infusion requests, laboratory test results, intraoperative blood loss, anesthesia duration, and intraoperative dexamethasone dosage. Intergroup comparisons of baseline patient characteristics and outcome variables were performed using either chi-squared tests or Fisher's exact tests for categorical variables and independent sample t tests or Wilcoxon rank-sum tests for continuous variables, as appropriate.

Multivariable linear regression models were used to analyze the relationship between preoperative smoking status, postoperative opioid consumption, postoperative pain scores, and number of IV-PCA infusion requests. Backward stepwise regression analyses with an entry criterion of a significance level of 0.05 and an exit criterion of 0.10 were used to determine independent explanatory factors for the study outcomes. Coefficients of determination (R^2) and adjusted R^2 values were calculated to evaluate the model fit. Regarding sample size estimation, the minimum number of cases for stepwise regression should be more than 40 × m, where m is the number of candidate variables in the model.[30,31] Given the sample size of 1162, this criterion was met in our analyses. Subgroup analyses by age ≥ or <65 years, sex, body mass index ≥ or <30 kg·m^{-2}, current sedative-hypnotic use, and general or neuraxial anesthesia, were also conducted to evaluate the association between current smoking and pain outcomes in these subgroups. Nonparametric Spearman's rank correlation analyses evaluated the potential dose-dependent association between smoking quantity, smoking duration, perioperative opioid consumption, pain scores, and number of IV-PCA infusion requests among current smokers. A two-sided significance level of 0.05 was used to define a significant difference. All statistical analyses were conducted using SAS software, version 9.4 (SAS Institute Inc., Cary, NC, USA).

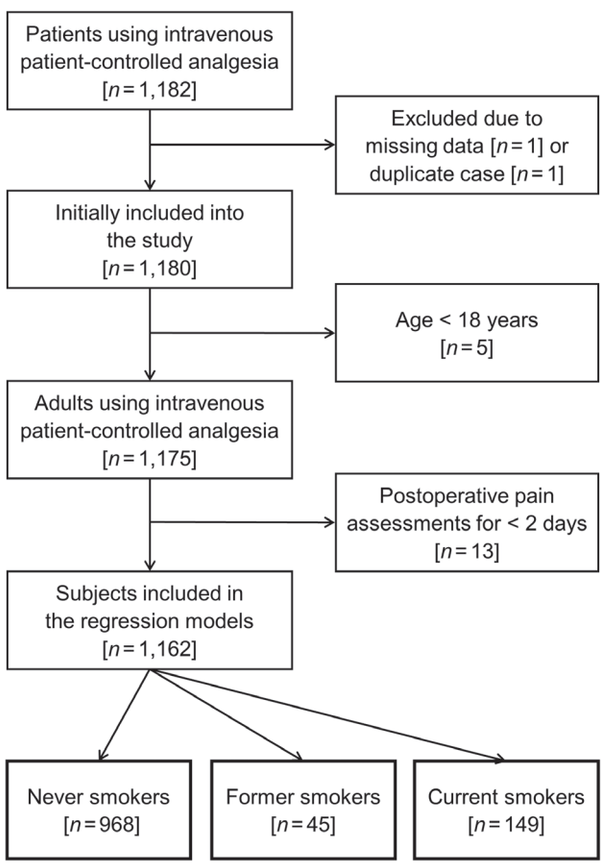

Fig. 1 Flow diagram for patient selection.

3. RESULTS

3.1. Baseline patient characteristics

A total of 1162 patients were included for analysis and were classified into never smokers (n = 968), former smokers (n = 45), and current smokers (n = 149) (Fig. 1). Table 1 shows the distribution of baseline patient and clinical characteristics for the three groups. The median duration of IV-PCA was 69.3 (IQR: 63.9-72.4), 68.9 (64.9-72.5), and 69.4 (64.9-72.5) hours in the never smokers, former smokers, and current smokers, respectively. The median total dosage of IV-PCA was 39.4 (IQR: 22.0-68.0), 46.4 (24.0-78.5), and 49.0 (30.0-75.1) mL in the never smokers, former smokers, and current smokers, respectively.

3.2. Smoking status and postoperative opioid consumption

Univariate analysis showed that current smokers had greater postoperative opioid consumption compared with never smokers, with a mean difference of 13.9 MME (95% confidence interval [CI], 4.4-23.3) (Table 2). There was no significant difference in postoperative opioid consumption between former and never smokers (mean difference: 7.4, 95% CI, –6.2 to 21.1) or current smokers (mean difference: –6.4, 95% CI, –24.6 to 11.8). Similarly, backward stepwise regression analyses demonstrated that current smoking was significantly associated with higher postoperative opioid consumption, regression coefficient (beta): 0.296 (95% CI, 0.068-0.523) (Table 3). Smoking quantity but not duration was significantly correlated with both intraoperative (Spearman's rho: 0.2207, p = 0.007) and postoperative opioid consumption (Spearman's rho: 0.1745, p = 0.033) (Table 4). Other independent factors for postoperative opioid consumption were age (beta: –0.019), sex (male vs female, beta: 0.354), surgical sites (head and neck vs extremity, beta: –0.939; upper abdomen vs extremity, beta: 0.890; lower abdomen vs extremity, beta: 0.393; spine vs extremity, beta: 0.521), laparoscopic or robotic surgery (beta: –0.475), type of anesthesia (general vs neuraxial anesthesia, beta: –0.346; combined vs neuraxial anesthesia, beta: –1.106), and anesthesia duration (beta: 0.219). In subgroup analyses, the association between current smoking and postoperative opioid consumption was significant among patients with age <65 years, female sex, body mass index <30 kg·m^{-2}, no current sedative-hypnotic use, and general anesthesia (Supplementary Table S2, http://links.lww.com/JCMA/A189).

3.3. Smoking status and postoperative pain scores

In univariate analysis, current smokers had higher mean daily maximum NRS pain scores compared with never smokers, mean difference: 0.2 (95% CI, 0.1-0.4) (Table 2). There was no significant difference in the postoperative pain scores between former and never smokers (0.2, –0.03 to 0.5) or current smokers (–0.02, –0.3 to 0.3). Postoperative pain scores were correlated with postoperative opioid consumption (Spearman's rho: 0.4766, p < 0.001) but not smoking quantity or duration (Table 4). Stepwise regression analyses showed that current smoking was significantly correlated with higher pain intensity compared with never smokers, beta: 0.087 (95% CI, 0.009-0.166) (Table 5). Other independent factors for pain scores were body mass index (beta: –0.007), current hypnotic use (beta: 0.067), surgical sites (head and neck vs extremity, beta: –0.259; upper abdomen vs extremity, beta: 0.155), and anesthesia duration (beta: 0.063). Subgroup analyses showed that the association between current smoking and pain intensity was significant in the subgroup of

Table 1

Baseline patient characteristics of the never, former, and current smokers

	Never smoker (n = 968)	Former smoker (n = 45)	Current smoker (n = 149)	p^a	p^b	p^c
Age, y	49.3 ± 15.9	56.5 ± 15.7	48.1 ± 14.1	0.391	0.003	<0.001
Sex, male	117 (12.1%)	31 (68.9%)	88 (59.1%)	<0.001	<0.001	0.235
Body mass index, kg·m^{-2}	26.2 ± 4.9	25.6 ± 4.2	25.1 ± 5.0	0.017	0.452	0.565
ASA class				0.250	0.173	0.570
I	168 (17.4%)	3 (6.7%)	19 (12.8%)			
II	780 (80.6%)	41 (91.1%)	125 (83.9%)			
III	20 (2.1%)	1 (2.2%)	5 (3.4%)			
Smoking quantity, cigarette per day	16 (10-20)	NA	NA	NA	NA	NA
Smoking duration, y	20 (10-30)	NA	NA	NA	NA	NA
Current alcohol drinking	44 (4.6%)	9 (20.0%)	44 (29.5%)	<0.001	<0.001	0.209
Current sedative-hypnotic use	202 (20.9%)	21 (46.7%)	43 (28.9%)	0.028	<0.001	0.026
Hypertension	240 (24.8%)	24 (53.3%)	33 (22.2%)	0.484	<0.001	<0.001
Diabetes mellitus	165 (17.1%)	12 (26.7%)	22 (14.8%)	0.488	0.097	0.066
Major depression	15 (1.6%)	1 (2.2%)	3 (2.0%)	0.723	0.519	>0.999
Malignancy	143 (14.8%)	17 (37.8%)	30 (20.1%)	0.092	<0.001	0.016
Preoperative blood test						
Hemoglobin, g·dL^{-1}	12.4 (11.1-13.5)	12.3 (10.6-13.9)	13.5 (11.9-14.8)	<0.001	0.825	0.004
Creatinine, mg·dL^{-1}	0.70 (0.61-0.84)	0.96 (0.74-1.18)	0.80 (0.66-0.97)	<0.001	<0.001	0.010
eGFR, mL·min·1.73 m^{-2}	97.2 (80.8-113.1)	79.6 (64.0-114.5)	100.7 (82.5-117.3)	0.147	0.029	0.015
Alanine aminotransferase, U·L^{-1}	18 (14-27)	22 (15-29)	21 (14-35)	0.042	0.261	0.794
Aspartate aminotransferase, U·L^{-1}	21 (17-26)	23 (19-28)	22 (17-34)	0.077	0.271	0.715
Surgical site				<0.001	<0.001	0.019
Extremity	176 (18.2%)	6 (13.3%)	53 (35.6%)			
Head and neck	7 (0.7%)	4 (8.9%)	4 (2.7%)			
Breast	22 (2.3%)	0 (0)	0 (0)			
Upper abdomen	82 (8.5%)	5 (11.1%)	22 (14.8%)			
Lower abdomen	601 (62.1%)	23 (51.1%)	45 (30.2%)			
Thorax	10 (1.0%)	3 (6.7%)	5 (3.4%)			
Spine	61 (6.3%)	3 (6.7%)	12 (8.1%)			
Other[d]	9 (0.9%)	1 (2.2%)	8 (5.4%)			
Laparoscopic or robotic surgery	117 (12.1%)	12 (26.7%)	22 (14.8%)	0.357	0.004	0.066
Intraoperative blood loss, mL	200 (50-600)	100 (10-300)	100 (10-250)	<0.001	0.057	0.457
Type of anesthesia				<0.001	0.071	0.025
Neuraxial anesthesia	348 (36.0%)	9 (20.0%)	10 (6.7%)			
General anesthesia	613 (63.3%)	36 (80.0%)	138 (92.6%)			
Combined general and neuraxial anesthesia	7 (0.7%)	0 (0)	1 (0.7%)			
Anesthesia duration, min	145 (100-228)	200 (135-285)	180 (130-250)	<0.001	0.004	0.323
Intraoperative dexamethasone, mg	5 (0-5)	5 (5-5)	5 (5-5)	<0.001	0.024	0.195
Peripheral nerve blockade	20 (2.1%)	0 (0)	4 (2.7%)	0.549	>0.999	0.575
Intraoperative opioid consumption, MME	10.0 (1.8-15.0)	11.5 (5.0-15.0)	12.5 (10.0-17.5)	<0.001	0.014	0.127
Initial IV-PCA infusion parameters						
Loading dose, mL	3.0 (2.0-3.0)	3.0 (0-3.0)	3.0 (2.0-4.0)	0.659	0.124	0.101
Demand dose, mL	1.1 (1.0-1.5)	1.0 (1.0-1.5)	1.2 (1.0-1.5)	0.177	0.711	0.295
Basal dose, mL·h^{-1}	0 (0-0)	0 (0-0)	0 (0-0)	0.328	0.214	0.590
Lockout interval, min	6 (5-8)	6 (5-8)	6 (5-8)	0.794	0.416	0.419
4-h dose limit, mL	24 (20-25)	25 (20-30)	25 (20-30)	0.163	0.205	0.705

Values are mean ± standard deviation, median (interquartile range), or counts (percent).

ASA = American Society of Anesthesiologists; eGFR = estimated glomerular filtration rate; MME = morphine milligram equivalent; NA = not applicable.

[a]Current smoker vs never smoker.

[b]Former smoker vs never smoker.

[c]Current smoker vs former smoker.

[d]Includes anal surgeries, hernia repair, and surgeries involving multiple sites.

male, body mass index <30 kg·m^{-2}, current sedative-hypnotic use, and general anesthesia (Supplementary Table S2, http://links.lww.com/JCMA/A189).

3.4. Number of IV-PCA infusion requests

Univariate analysis showed that current smokers had more infusion requests compared with never smokers (Table 2). Stepwise regression models demonstrated that current smoking was significantly correlated with a greater number of infusion requests (beta: 0.391; 95% CI, 0.073-0.710) compared with never smokers (Table 6). Independent factors for infusion request numbers were age (beta: –0.014), sex (male vs female, beta: 0.437), hemoglobin level (beta: –0.491), surgical sites (head and neck vs extremity, beta: –1.097; breast vs extremity, beta: –0.910; upper abdomen vs extremity, beta: 1.131; lower abdomen vs extremity, beta: 0.524; spine vs extremity, beta:

Table 2

Postoperative opioid consumption, pain scores, and numbers of IV-PCA infusion requests

	Never smoker n = 968)	Former smoker (n = 45)	Current smoker (n = 149)	p^a	p^b	p^c
Postoperative opioid consumption, MME	39.4 (22.0-68.0)	46.4 (24.0-78.5)	49.0 (30.0-75.1)	0.003	0.397	0.463
	50.3 ± 45.4	57.7 ± 48.6	64.2 ± 55.8			
Mean daily maximum NRS pain score	2.9 (2.4-3.5)	3.0 (2.8-3.8)	3.1 (2.5-3.8)	0.005	0.069	0.824
	2.9 ± 0.8	3.2 ± 0.9	3.2 ± 0.9			
Daily maximum NRS pain score						
POD0, at rest	3.0 (2.0-4.0)	3.0 (2.0-4.0)	3.0 (2.0-4.0)	0.051	0.773	0.422
	2.9 ± 1.7	2.9 ± 1.4	3.2 ± 1.6			
POD0, during movement	5.0 (4.0-6.0)	5.0 (4.0-6.0)	5.0 (4.0-6.0)	0.025	0.611	0.458
	4.6 ± 2.0	4.8 ± 1.9	5.1 ± 1.8			
POD1, at rest	2.0 (1.0-3.0)	2.0 (2.0-3.0)	2.0 (1.0-3.0)	0.932	0.201	0.280
	2.3 ± 1.3	2.6 ± 1.3	2.4 ± 1.5			
POD1, during movement	4.0 (3.0-5.0)	4.0 (3.0-6.0)	5.0 (3.0-6.0)	0.341	0.670	0.982
	4.5 ± 1.7	4.7 ± 1.9	4.7 ± 1.8			
POD2, at rest	2.0 (1.0-2.0)	2.0 (1.0-2.0)	2.0 (1.0-3.0)	0.032	0.301	0.794
	1.7 ± 1.1	2.0 ± 1.4	1.9 ± 1.1			
POD2, during movement	4.0 (3.0-5.0)	4.0 (3.0-4.5)	4.0 (3.0-5.0)	0.119	0.909	0.495
	3.7 ± 1.6	3.8 ± 1.9	3.9 ± 1.8			
POD3, at rest	1.0 (0.0-2.0)	1.0 (1.0-2.0)	1.0 (1.0-2.0)	0.143	0.030	0.184
	1.1 ± 1.0	1.4 ± 1.1	1.2 ± 1.0			
POD3, during movement	2.0 (2.0-3.0)	3.0 (2.0-4.0)	3.0 (2.0-4.0)	0.021	0.016	0.283
	2.6 ± 1.5	3.2 ± 1.5	2.9 ± 1.6			
Number of IV-PCA infusion requests	37 (18-77)	39 (14-89)	54 (27-97)	0.002	0.842	0.224
	75 ± 211	80 ± 118	81 ± 91			
Number of IV-PCA injection denials	9 (1-31)	13 (3-41)	20 (5-41)	<0.001	0.243	0.518
	43 ± 203	49 ± 101	44 ± 76			
Use of ketorolac	7 (0.7)	0 (0)	1 (0.7)	>0.999	>0.999	>0.999

Values are median (interquartile range), mean ± standard deviation, or counts (percent). Continuous variables were compared between groups using Wilcoxon rank-sum tests.
IV-PCA = intravenous patient-controlled analgesia; MME = morphine milligram equivalent; NRS = numeric rating scale; POD = postoperative day.
[a]Current smoker vs never smoker.
[b]Former smoker vs never smoker.
[c]Current smoker vs former smoker.

Table 3

Independent factors for postoperative opioid consumption

	Unstandardized beta (95% CI)	SE	Standardized beta	p
Smoking status				0.031
Former vs never smoker	0.073 (–0.300 to 0.445)	0.190	0.011	0.703
Current vs never smoker	0.296 (0.068-0.523)	0.116	0.079	0.011
Age, y	–0.019 (–0.025 to –0.014)	0.003	–0.245	<0.001
Sex, male vs female	0.354 (0.143-0.565)	0.108	0.114	0.001
Current sedative-hypnotic use	0.162 (–0.013 to 0.337)	0.089	0.055	0.070
Surgical site				<0.001
Head and neck vs extremity	–0.939 (–1.565 to –0.314)	0.319	–0.085	0.003
Breast vs extremity	–0.518 (–1.039 to 0.003)	0.265	–0.057	0.051
Upper abdomen vs extremity	0.890 (0.606-1.174)	0.145	0.208	<0.001
Lower abdomen vs extremity	0.393 (0.182-0.604)	0.107	0.156	<0.001
Thorax vs extremity	–0.131 (–0.696 to 0.434)	0.288	–0.013	0.649
Spine vs extremity	0.521 (0.211-0.832)	0.158	0.103	0.001
Other vs extremity	0.373 (–0.188 to 0.934)	0.286	0.037	0.192
Laparoscopic or robotic surgery	–0.475 (–0.700 to –0.250)	0.115	–0.128	<0.001
Type of anesthesia				<0.001
General vs neuraxial anesthesia	–0.346 (–0.536 to –0.156)	0.097	–0.130	<0.001
Combined vs neuraxial anesthesia	–1.106 (–1.945 to –0.267)	0.428	–0.073	0.010
Anesthesia duration, min[a]	0.219 (0.106-0.331)	0.057	0.133	<0.001

Factors with beta > 0 increased postoperative opioid consumption and those with beta < 0 reduced it. Model fit: $R^2 = 0.1478$, adjusted $R^2 = 0.1352$.
Beta = regression coefficient; CI = confidence interval; SE = standard error of regression coefficient.
[a]On base-2 logarithmic scale.

0.675), and laparoscopic or robotic surgery (beta: –0.469). In subgroup analyses, the association between current smoking and number of IV-PCA infusion requests was significant among patients with age <65 years, female sex, body mass index <30 kg·m^{-2}, no current sedative-hypnotic use, and general anesthesia (Supplementary Table S2, http://links.lww.com/JCMA/A189).

Table 4

Correlation between smoking quantity, smoking duration, perioperative opioid consumption, postoperative pain scores, and numbers of IV-PCA infusion requests among the current smokers

	Smoking quantity	Smoking duration	Intraoperative opioid consumption	Postoperative opioid consumption	Total opioid consumption	Mean daily maximum NRS pain score	Number of IV-PCA infusion requests
Smoking quantity							
Spearman's rho	1.0000	0.1216	0.2207[b]	0.1745[a]	0.1981[a]	0.0683	0.0797
p	NA	0.140	0.007	0.033	0.016	0.408	0.355
Smoking duration							
Spearman's rho	0.1216	1.0000	–0.0053	–0.1104	–0.1016	–0.0107	–0.0167
p	0.140	NA	0.949	0.180	0.218	0.897	0.844
Intraoperative opioid consumption							
Spearman's rho	0.2207[b]	–0.0053	1.0000	0.1549	0.3701[c]	0.1605	–0.0659
p	0.007	0.949	NA	0.059	<0.001	0.051	0.425
Postoperative opioid consumption							
Spearman's rho	0.1745[a]	–0.1104	0.1549	1.0000	0.9543[c]	0.4766[c]	0.7568[c]
p	0.033	0.180	0.059	NA	<0.001	<0.001	<0.001
Total opioid consumption							
Spearman's rho	0.1981[a]	–0.1016	0.3701[c]	0.9543[c]	1.0000	0.4814[c]	0.6832[c]
p	0.016	0.218	<0.001	<0.001	NA	<0.001	<0.001
Mean daily maximum NRS pain score							
Spearman's rho	0.0683	–0.0107	0.1605	0.4766[c]	0.4814[c]	1.0000	0.3438[c]
p	0.408	0.897	0.051	<0.001	<0.001	NA	<0.001
Number of IV-PCA infusion requests							
Spearman's rho	0.0797	–0.0167	–0.0659	0.7568[c]	0.6832[c]	0.3438[c]	1.0000
p	0.355	0.844	0.425	<0.001	<0.001	<0.001	NA

IV-PCA = intravenous patient-controlled analgesia; NA = not applicable; NRS = numeric rating scale.
[a]$p < 0.05$.
[b]$p < 0.01$.
[c]$p < 0.001$.

Table 5

Independent factors for postoperative pain intensity

	Unstandardized beta (95% CI)	SE	Standardized beta	*p*
Smoking status				0.010
Former vs never smoker	0.095 (–0.038 to 0.228)	0.068	0.041	0.162
Current vs never smoker	0.087 (0.009-0.166)	0.040	0.065	0.029
Body mass index, kg·m^{-2}	–0.007 (–0.012 to 0.002)	0.003	–0.079	0.007
Current sedative-hypnotic use	0.067 (0.004-0.131)	0.032	0.063	0.037
Surgical site				0.181
Head and neck vs extremity	–0.259 (–0.490 to 0.027)	0.118	–0.066	0.028
Breast vs extremity	–0.109 (–0.301 to 0.083)	0.098	–0.033	0.265
Upper abdomen vs extremity	0.155 (0.054-0.255)	0.051	0.101	0.003
Lower abdomen vs extremity	0.023 (–0.043 to 0.090)	0.034	0.026	0.496
Thorax vs extremity	–0.122 (–0.333 to 0.088)	0.107	–0.034	0.255
Spine vs extremity	0.041 (–0.075 to 0.156)	0.059	0.023	0.487
Other sites vs. extremity	0.154 (–0.056 to 0.364)	0.107	0.043	0.150
Anesthesia duration, min[a]	0.063 (0.027-0.099)	0.018	0.107	<0.001

Factors with beta > 0 increased postoperative pain scores and those with beta < 0 reduced them. Model fit: $R^2 = 0.0568$, adjusted $R^2 = 0.0469$.
Beta = regression coefficient; CI = confidence interval; SE = standard error of regression coefficient.
[a]On base-2 logarithmic scale.

4. DISCUSSION

In this retrospective cohort study, we found that current cigarette smoking was significantly associated with greater postoperative opioid consumption and pain intensity after adjusting for a variety of covariates. In addition, smoking quantity was significantly positively correlated with both intraoperative and postoperative opioid requirements. Current smokers requested more opioid infusions during IV-PCA compared with never smokers. There was no significant difference in the postoperative pain outcomes between former and never smokers. The present study had two strengths for evaluating the putative effect of tobacco smoking on opioid requirement and pain severity. First, we included patients using IV-PCA to accurately calculate opioid dosage and to ensure that the same pain service staff assessed the pain scores. Second, opioid dosage, pain scores, and infusion request numbers were analyzed, clarifying the potential influence of active smoking on opioid seeking behavior, opioid consumption, and pain intensity.

Previous studies reported inconsistent results regarding the relationship between cigarette smoking and opioid consumption or pain intensity.[11–22] Our study showed that current smoking was associated with higher opioid requirements and increased

Table 6

Independent factors for numbers of IV-PCA infusion requests

	Unstandardized beta (95% CI)	SE	Standardized beta	*p*
Smoking status				0.077
Former vs never smoker	−0.072 (−0.602 to 0.458)	0.270	−0.008	0.791
Current vs never smoker	0.391 (0.073-0.710)	0.162	0.076	0.016
Age, y	−0.014 (−0.021 to −0.006)	0.004	−0.123	<0.001
Sex, male vs female	0.437 (0.133-0.741)	0.155	0.102	0.005
Hemoglobin, g·dL^{-1}[a]	−0.491 (−0.911 to −0.072)	0.214	−0.070	0.022
Surgical site				<0.001
Head and neck vs extremity	−1.097 (−1.977 to −0.218)	0.448	−0.072	0.015
Breast vs extremity	−0.910 (−1.643 to −0.178)	0.373	−0.073	0.015
Upper abdomen vs extremity	1.131 (0.726-1.536)	0.206	0.193	<0.001
Lower abdomen vs extremity	0.524 (0.221-0.828)	0.155	0.151	<0.001
Thorax vs extremity	−0.310 (−1.107 to 0.487)	0.406	−0.022	0.446
Spine vs extremity	0.675 (0.242-1.108)	0.221	0.098	0.002
Other vs extremity	−0.142 (−0.943 to 0.659)	0.408	−0.010	0.728
Laparoscopic or robotic surgery	−0.469 (−0.780 to −0.157)	0.159	−0.092	0.003

Factors with beta > 0 increased numbers of IV-PCA infusion requests and those with beta < 0 reduced them. Model fit: R^2 = 0.0932, adjusted R^2 = 0.0820.

Beta = regression coefficient; CI = confidence interval; SE = standard error of regression coefficient.

[a]On base-2 logarithmic scale.

pain intensity after major surgery, agreeing with some previous studies[11–14,16–20,22] but not others.[15,21] Most prior studies restricted their patient population to specific types of surgery (ie, abdominal,[11,19] orthopedic,[12,17,21] thoracic,[15,16] oculoplastic,[18] and cesarean section),[22] limiting the generalizability of the study results. In a matched cohort study, Etcheson et al[17] demonstrated significantly higher opioid consumption among smokers compared with nonsmokers after total hip arthroplasty. However, the pain intensity was comparable between the two groups. Steinmiller et al[21] reported that active smokers using IV-PCA after orthopedic surgery had more infusion requests and injection denials but the total opioid dosage was similar to that of nonsmokers. In a case series analysis, Marco et al[22] reported that female smokers who underwent a cesarean section required more postoperative morphine compared with their counterparts without a smoking history. However, pain severity was similar within the 24 hours after the use of IV-PCA. These discrepancies might result from inadequate patient samples and heterogeneity in IV-PCA infusion settings and outcome assessment methods.[17,21,22] The present study observed a dose-dependent association between smoking quantity and perioperative opioid consumption, contrasting with one previous study.[15] Oh et al[15] analyzed patients undergoing lung resections for lung cancer or esophagectomy for esophageal cancer and reported a non-significant correlation between cigarette smoking pack-years and postoperative opioid dosage. The mixed groups of never, former, and current smokers and greater surgical invasiveness were potentially responsible for the conflicting findings.[15]

The association between cigarette smoking and pain outcomes probably results from the biological effect of nicotine. Nicotine exerts short-acting analgesic effects, associated with the activation of α4β2 nAChR, which is widely distributed throughout the central and peripheral nervous systems.[32,33] Daily smokers reported higher spontaneous pain after 12 to 24 hours of nicotine deprivation.[10,34] It has been postulated that the deprived state increases pain sensitivity through both central (eg, enhanced excitability of spinal dorsal horn neurons, release of pain-related neurotransmitters, and nAChR availability) and peripheral (eg, vasodilation by neuropeptide release from peripheral C-fiber activation) processes.[35,36] Moreover, activating endogenous opioid systems and releasing beta-endorphins may also contribute to nicotine-analgesic effects.[10,37] A Cochrane meta-analysis demonstrated that preoperative intranasal or transdermal nicotine treatments did not affect postoperative opioid requirements within 24 postoperative hours but significantly reduced postoperative pain scores by a mean −0.88 on a 0 to 10 point scale at postoperative 24 hours.[38] Nevertheless, considering the low quality and substantial result heterogeneity of the included studies, the relationship between nicotine and pain outcomes remains uncertain.[38] The effect of nicotine on opioid requirements and pain perception is multifaceted. Current evidence suggests that nicotine has antinociceptive effects for nonsmokers, but in current smokers, nAChR desensitization and nicotine withdrawal limit the analgesic benefits of perioperative nicotine.[10,37] In an animal study, Loney et al[39] demonstrated that pretreatment with nicotine promoted opioid intake, which partly acted within the insular cortex to obscure unwilling opiate memories. Another study indicated that morphine regulated the activity of inhibitory interneurons within the frontal cortex and these actions on interneurons might be required for morphine contextual place conditioning.[40] Nicotinic modulation of GABAergic interneurons impaired the synaptic potentiation within the insular cortex, caused a deficit in learning about drug-associated contexts, and facilitated morphine demands.[39,40] Our subgroup analyses demonstrated that current smoking was associated with greater postoperative opioid consumption among patients who were aged <65 years and female. Our previous study showed that female patients had a higher baseline level of postoperative pain intensity compared with males, and older patients had faster pain resolution compared with younger patients.[25] Sex and age differences in pain sensitivity and trajectory might explain the present results.

Our findings suggested that tobacco smoking is a potentially modifiable factor for opioid requirements and pain severity after surgery. In addition to preventing wound infection and cardiovascular complications,[41] smoking cessation should be encouraged before surgery to reduce opioid use and opioid-related adverse events. Our analyses showed that the difference in mean daily maximum pain scores between current and never smokers was just 0.2, which probably represents a low clinical significance in daily practice. Nevertheless, since pain intensity is an important influential factor for opioid requirement, multimodal analgesia with nonopioid analgesics and techniques should be considered for active smokers to reduce opioid use.[42,43] Finally, large-scale high-quality clinical trials are needed to evaluate the analgesic benefits of nicotine treatments for improving postoperative pain control.

There were several limitations to this study. First, this was a retrospective study, and therefore some potential confounding factors might not be available in our electronic medical database. Although our multivariable models have adjusted for a list of demographic and clinical factors, residual confounding is still possible. Second, the sample size of former and current smokers was modest, which precludes propensity score matching analyses. Third, postoperative opioid use was measured only in the immediate postoperative period. Whether cigarette smoking affects long-term opioid use or chronic pain rates after surgery remains unclear. Fourth, we did not evaluate patients using electronic cigarettes, which have been partly replacing traditional cigarettes, especially in younger populations.[44] Fifth, the IV-PCA infusion parameters were not standardized, and the variability in dosage settings might cause variations in opioid consumption and pain scores across the three groups. Well-designed prospective studies are warranted to better elucidate the impact of active smoking on postoperative pain outcomes. Last, we did not analyze the relationship between smoking cessation and pain outcomes. This requires additional studies to clarify the minimal threshold duration of smoking cessation to improve perioperative pain management.

In conclusion, this study demonstrated that current smoking was associated with increased postoperative opioid consumption, pain intensity, and numbers of IV-PCA infusion requests. Additionally, there was a graded relationship between smoking quantity and perioperative narcotic requirements among current smokers. These results suggested that smoking cessation and nonopioid analgesia strategies are needed for surgical patients who are actively smoking. Our findings provided important evidence for improving postoperative pain control for active smokers. Further studies are needed to clarify the biological mechanism of our statistical findings, to examine the analgesic effect of nicotine treatments, and to determine the optimal interval of smoking abstinence before surgery.

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APPENDIX A. SUPPLEMENTARY DATA

Supplementary data related to this article can be found at http://links.lww.com/JCMA/A189.

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