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REVIEW

The Effect of Smoking Cessation on Acute Pain: A Systematic Review

Matias Ignacio Vega Palma · Christoph Klivinyi · Thomas Lampl · Kordula Lang-Illievich · Helmar Bornemann-Cimenti · Istvan S. Szilagyi

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ABSTRACT

Smoking is a known risk factor for developing various pain-related disorders. However, acute pain often triggers the craving for cigarette consumption, resulting in a positive feedback mechanism. In addition, there is evidence of decreased pain tolerance during the early stages of abstinence. Therefore, in this study, we aimed to investigate whether a period of decreased pain tolerance and increased pain intensity occurs during smoking cessation. A systematic literature search was conducted through PubMed and Web of Science databases for controlled studies investigating the influence of smoking cessation on acute (defined as pain presentation of < 3 months) and postoperative pain. The outcomes of interest included pain perception threshold, pain tolerance, pain intensity, and postoperative opioid requirements. The search strategy yielded 1478 studies, of which 13 clinical studies met our inclusion criteria. The included studies collectively represented data from 1721 participants from four countries. Of these, 43.3% of the included individuals were females. The mean age of the included subjects was 44.2 ± 8.2 years. The duration of smoking cessation varied considerably. The shortest duration was 2 h; others investigated the effect after more than 1 month of smoking cessation. Smokers had a history of 14.6 ± 9.9 years of nicotine abuse. The mean number of daily smoked cigarettes was 17.5 ± 10.3. Most studies examined in this systematic review show a negative influence of smoking cessation on acute pain. However, the affected pain modalities, the duration of the altered pain perception, and whether male and female smokers are equally affected could not be ascertained due to high heterogeneity and few available studies.

Keywords: Smoking; Tobacco; Cessation; Pain; Acute; Postoperative

Matias Ignacio Vega Palma and Christoph Klivinyi contributed equally.

M. I. Vega Palma · C. Klivinyi · T. Lampl · K. Lang-Illievich · H. Bornemann-Cimenti (✉) · I. S. Szilagyi
Department of Anaesthesiology and Intensive Care Medicine, Medical University of Graz, Auenbruggerplatz 5/5, 8036 Graz, Austria
e-mail: helmar.bornemann@medunigraz.at

Key Summary Points

The effect of smoking on pain is complex: while chronic tobacco use is associated with a higher rate of chronic pain, nicotine has analgetic properties.

Little is known on the effect of smoking cessation on pain perception.

Our systematic reviews assessed 13 clinical studies on pain after smoking cessation.

Most studies showed that cigarette withdrawal leads to a phase of decreased pain tolerance and increased pain intensity.

Our results warrant increased attention and care for pain management among patients in the acute phase of nicotine withdrawal.

INTRODUCTION

Tobacco is the most widely abused substance and the leading cause of morbidity and mortality, with 1.3 billion adult smokers globally in 2020 [1–3]. Furthermore, smoking is one of the best-studied risk factors for cardiovascular diseases [1, 4, 5], several types of cancer [6–8], infections [9], and diseases associated with maladaptive immune responses [10]. In addition, smoking is a well-known risk factor for acute and chronic pain [11, 12]. For example, chronic low back pain occurs more frequently in smokers than in the normal population due to reduced blood supply to the intervertebral discs and associated degenerative changes [13]. Similarly, smokers are more likely to be affected by knee pain due to cartilage defects, and decreased cartilage substances are associated with a positive smoking history [14]. Recent evidence also presents smoking as a risk factor for cluster headaches [15]. Furthermore, smokers experience more pain and functional limitations regardless of the disease than non-smokers [16].

At the same time, acute pain often triggers the craving for cigarette consumption, resulting in a positive feedback mechanism [17]. There are over 9000 chemical substances in tobacco smoke, of which nicotine is the most psychoactive substance and most strongly associated with the development of addiction [18]. Some studies show that nicotine has a transient analgesic effect. This effect could be influenced by gender, type of pain stimulus, and nicotine dose [16]. While constant analgesic effects can be demonstrated with conditioned pain modulation, no difference in pain tolerance is apparent with heat or electrical stimuli. Systemic nicotine administration also reduces postoperative pain, as demonstrated in several studies [19–21]. These results highlight the positive feedback mechanism of nicotine—smoking reduces acute pain, positively reinforcing smoking behavior [16].

In addition to a direct analgesic effect of nicotine via agonism at nicotinic acetylcholine receptors (nAChR) [22], it may influence pain perception through the endocrine system, more specifically by activating the hypothalamic–pituitary–adrenal axis. Physiologically this may occur during stressful situations and can increase pain threshold as well as decrease pain sensitivity [23]. Nicotine also leads to activation of the axis, but long-term use leads to desensitization and the development of tolerance [16].

Although the role of smoking on the pathophysiology of acute pain has been well researched and extensively reviewed [16, 24–31], the effect of tobacco withdrawal on pain-related outcomes is yet to be thoroughly investigated. Several studies show a decrease in pain perception after sustained tobacco withdrawal [32, 33]; at the same time, there is evidence of reactively decreased pain tolerance during the early stages of abstinence [17]. This characteristic has implications for several areas of medicine. For instance, among patients with short-term tobacco abstinence undergoing surgery, a change in pain tolerance may result in increased pain and a lower quality of postoperative recovery [34]. Given such broad implications of changes in pain-related outcomes with

smoking cessation, this systematic review aims to evaluate whether a period of decreased pain tolerance and increased pain intensity occurs with smoking cessation.

METHODS

A systematic literature search was conducted for controlled studies investigating the influence of smoking cessation on acute and postoperative pain in PubMed and Web of Science databases. The search strategy combined terms for smoking and study designs with expressions for pain that have been previously described [35] and are summarized in Table 1. Furthermore, this study's protocol was published and is accessible from the Open Science Foundation Registries [36].

Potentially relevant literature identified during our initial search was imported into the web app "Rayyan QCRI" for the screening process after removing duplicates. Two reviewers (T.L., K.L.I.) independently screened the literature, with a third reviewer (H.B.C.) mediating in case of conflicting decisions. Acute pain was defined as the duration since the onset of pain of no more than 3 months, including but not limited to postoperative pain and experimental pain models. The population of interest included male and female smokers. Smoking cessation interventions were defined as all interventions aimed at smoking abstinence. The outcome was defined as pain-relevant parameters (pain perception threshold, pain tolerance, and pain intensity) and postoperative opioid requirements. In case of missing data in the original reports, authors were contacted with a request for providing unreported data. The studies were included from 1970 to 2022. The latest literature search was conducted in July 2022.

This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

RESULTS

The search strategy yielded 1478 papers, of which 1402 were excluded after title screening and another 63 subsequently excluded after the abstract screening. Finally, 13 studies meeting our inclusion criteria were selected for full-text screening. A flowchart of the study is shown in Fig. 1. The details of the studies are summarized in Table 2.

Only two studies were designed as randomized controlled trials; five are nonrandomized trials. Six studies are cohort studies. The included studies collectively represented data four countries: the USA (n = 8), China (n = 3), Pakistan (n = 1), and the Republic of Korea (n = 1). The oldest study was published in 2000 [34], and the rest were published between 2004 and 2021 [3, 17, 37–46].

The collective study population included 1721 participants. Overall, 43.3% of the

Table 1 Search strategy

Theme	Search terms
#1 Smoking abstinence	Smoking OR cessation OR Nicotine OR Tobacco OR abstinence OR withdrawal OR deprivation OR abstinent OR deprived
#2 Pain	allodyn* OR analg* OR arthralg* OR brachialg* OR causalg* OR cephalalg* OR cephalea OR cervicodyn* OR colic OR eudyn* OR fibromyalg* OR headache OR hyperalg* OR hypoalg* OR hyperpath* OR maldyn* OR migraine OR neuralg* OR nocicept* OR odontalg* OR ophthalmodyn* OR vulvodyn* OR otalg* OR pain* OR radicul* OR toothache OR orchidodyn* OR coccygodyn* OR CRPS OR nuchalg* OR lumbalg* OR lumboischialg* OR cervicobrachial*
#3 Study type	trial OR study OR placebo OR control* OR RCT

The search was conducted by combining #1, #2, and #3 using the AND operator

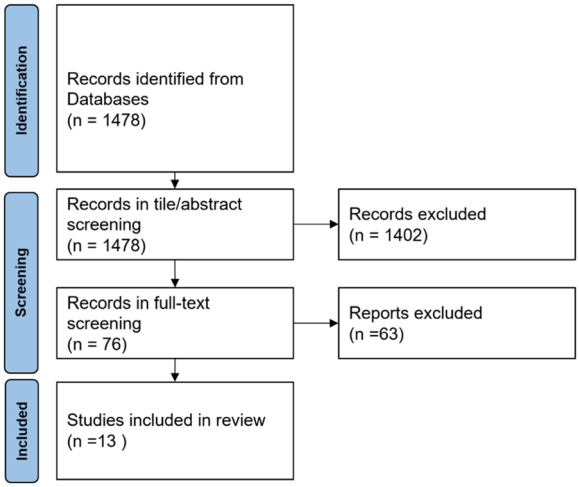

Fig. 1 Flowchart of the screening process

included individuals were females. Three studies presented data exclusively from males [41, 45, 46], one from females [34], and one did not report gender outcomes [44]. One paper dealt with pain in adolescents aged 14–18 years [37], while the remaining dealt with adult patients, some without age limitations [38, 43]. The mean age of the included subjects was 44.2 ± 8.2 years.

The duration of smoking cessation varied considerably. The shortest duration was 2 h [3]; others investigated the effect after more than 1 month of smoking cessation [41, 44]. Smokers had a history of 14.6 ± 9.9 years of nicotine abuse. The mean number of daily smoked cigarettes was 17.5 ± 10.3.

Different modalities were used to induce pain. Two studies investigated spontaneous pain [38, 42]; one study used a capsaicin pain model [17], and one used radiant heat pain [3]. Some studies assessed pain threshold: three assessed cold pain threshold [37, 39, 43], one heat pain threshold [43], and one electrical pain threshold [45]. Six studies investigated the effect of smoking cessation on postoperative pain levels and opioid requirement [34, 40, 41, 44–46]. The details of this group of studies are presented in Table 3.

DISCUSSION

Our systematic literature search identified 13 clinical studies assessing pain development after smoking cessation. Most studies show that cigarette withdrawal leads to a phase of decreased pain tolerance as well as increased pain intensity. Only Cosgrove found that smoking withdrawal and the subsequent higher nicotinic acetylcholine receptors AChRs containing the b2* subunit (b2*-nAChR) availability were associated with increased pain sensitivity but not pain tolerance [39]. However, there was a high degree of heterogeneity among the examined studies regarding methodology. For instance, different pain tests were utilized, the duration of smoking cessation differed, and several different pain-related outcome parameters were considered. These factors must, of course, be considered when trying to derive generalizations. Nevertheless, some of these findings merit detailed discussion.

Outcome Parameters

Regarding outcome parameters, four studies showed a decreased tolerance to the pain test performed during smoking cessation [3, 37, 39, 43]. In addition, a decrease in the pain perception threshold was reported in three studies [39, 42, 45]. Three studies show increased pain intensity during nicotine withdrawal [17, 37, 38]. Comparing these findings led us to question whether the modality of pain influences the perception of pain during withdrawal. For example, pain triggered by cold [37, 39] seems to lead more consistently to an increased perception than heat-induced pain [43].

Time Course

The initiation timepoint for the change in pain perception after smoking cessation and the duration of the effect have immense clinical relevance. However, due to the methodological heterogeneity, only limited conclusions could be drawn. Five studies documented an increased pain perception between 12 and 48 h after

Table 2 Study characteristics

Author (year)	Country	Study design	Participants	Gender	Age (years)	Smoking dose	Groups	Pain-related outcomes	Results
Woodside (2000)	China	Retrospective cohort study	$n = 169$	100% female	36.3 ± 5.3	n.r.	(A) Nonsmokers (B) < 1 month smoke abstinence (C) Current smokers	Postoperative opioid requirement 12 h after gynecological surgery	Nonsmokers had a significantly lower opioid requirement ($p < 0.02$) than groups B and C
Creekmore (2004)	USA	Retrospective cohort study	$n = 89$	27.0% female	65.0 ± 10.7	Minimum 10 cigarettes per day, minimum 1 year	(A) Current smoker (< 7 days abstinent) (B) Nonsmokers	Measurement of postoperative opioid requirement in patients going through CABG	Group A required 23% ($p = 0.027$) and 33% ($p = 0.023$) more opioids than group B relative to their body weight and BMI
Cosgrove (2010)	USA	Controlled study	$n = 24$	45.8% females	34.6 ± 11.4	18.0 ± 6.5 cigarettes per day, 14.6 ± 9.0 years	1 group of smokers	Pain stimulus through CPT 3-4 h and 7–13 days after the last cigarette	Pain intensity and tolerance are limited during withdrawal, however not statistically significant ($p = 0.14$ and 0.1)
Nakajima (2014)	USA	Controlled study	$n = 135$	47.4% females	33.9 ± 2.0	18.3 ± 10 cigarettes per day, 11.3 ± 1.4 years	(A) 48 h nicotine deprivation (B) Nonsmokers	Pain stimulus application through (a) CPT and (b) HPT	Pain tolerance after CPT in group A reduced compared with group B ($p < 0.01$)
Baiamonte (2016)	USA	Controlled study	$n = 37$	48.6% females	19.8 ± 0.4	8.7 ± 1.5 cigarettes per day	(A) > 2 h nicotine deprivation (B) Nonsmokers	Pain stimulus application through radiant heat test	Significantly decreased pain tolerance among smokers under withdrawal compared to non-smokers ($p < 0.01$)
Bagot (2017)	USA	Controlled study	$n = 96$	53% females	16.0 ± 1.4	13.2 ± 7.0 cigarettes per day, 2.4 ± 1.7 years	(A) Current smokers (B) Nonsmokers	Current smokers received a CPT 30 h and 42 h after nicotine abstinence	Pain tolerance after nicotine abstinence was reduced ($p < 0.001$)
Shen (2017)	China	Retrospective cohort study	$n = 148$	0% female	49.9 ± 10.0	n.r.	(A) Nonsmokers (B) < 1 month smoke abstinence	Electrical pain threshold, Measurement of the postoperative opioid requirement (rescue analgesia and PCA) through VAS in the first 48 h after liver resection surgery	Abstinent tobacco smokers exhibited lower pain thresholds before surgery and demanded a larger quantity of opioids during the first 48 h after surgery than nonsmokers

Table 2 continued

Author (year)	Country	Study design	Participants	Gender	Age (years)	Smoking dose	Groups	Pain-related outcomes	Results
Bello (2018)	USA	Controlled study	$n = 214$	44.1% females	47.7 ± 11,0	14.4 ± 6.7 cigarettes per day	1 group of current smokers with chronic pain	Acute pain measurement after 16 h nicotine abstinence versus ad libitum smokers through NRS (0–10) (every participant underwent both interventions)	Acute pain after nicotine abstinence was significantly higher ($p = 0.01$)
Ditre (2018)	USA	RCT	$n = 165$	43% female	41.1 ± 12.7	22 ± 13 cigarettes per day, 24 ± 12.5 years	(A) 12–24 nicotine deprivation (B) 2 h nicotine deprivation (C) Ad libitum smoker	Capsaicin solution application	Significant increase in pain intensity and inflammation area in groups A and B compared with ad libitum smokers
LaRowe (2018)	USA	RCT	$n = 137$	44% female	40.2 ± 12.4	22 ± 13 cigarettes per day, 23.2 ± 12.2 years	(A) 12–24 h nicotine deprivation (B) Ad libitum smoker	Spontaneous pain intensity (NRS, 0–10)	Pain in group A 3.5 times more often ($p < 0.05$) and stronger ($p < 0.01$) than in group B
Zhao (2018)	China	Prospective cohort study	$n = 107$	0% female	64.3 ± 2.3	n.r.	(A) < 3 weeks smoke abstinence (B) > 3 weeks smoke abstinence (C) Nonsmokers	Measurement of opioid requirement after radical thoracoscopic resection of lung cancer	The opioid requirement was significantly higher in patients with < 3 weeks of abstinence ($p < 0.05$) compared with groups B and C. Group B had significantly higher opioid requirements than group C
Kim (2021)	Republic of Korea	Retrospective cohort study	$n = 144$	0% female	57.9 ± 10.9	24.5 ± 14.5 PY	(A) Nonsmoker (B) < 1 month nicotine abstinence (C) > 1 month nicotine abstinence	Postoperative opioid requirement after laparoscopic distal gastrectomy with gastroduodenostomy surgery	The opioid requirement was significantly higher in patients with < 1 month of abstinence ($p < 0.001$)

Table 2 continued

Author (year)	Country	Study design	Participants	Gender	Age (years)	Smoking dose	Groups	Pain-related outcomes	Results
Nazir (2021)	Pakistan	Prospective cohort study	*n* = 256	n.r.	n.r.	13.3 ± 10.6 years, 10.3 ± 14.7 PY,	(A) Smoking cessation < 2 days (B) 3–7 days (C) 8 days to 4 weeks (D) > 4 weeks	Measurement of intraoperative hemodynamics, postoperative pain, and postoperative hospital stay after scheduled noncardiac surgery	Mean postoperative pain increased in patients with smoking cessation for 48 h, as compared with the patients with duration of cessation of more than 4 weeks

BMI body mass index, *CABG* coronary artery bypass surgery, *CPT* cold pressor test, *HPT* heat pain tolerance, *NRS* numeric rating scale, *n.r.* not reported, *PCA* patient-controlled analgesia, *PY* pack years, *RCT* randomized controlled trial, *VAS* visual analog scale

nicotine withdrawal [17, 37, 38, 42, 43], while Bagot demonstrated a reduction in pain tolerance and an increase in pain intensity as early as 30 min after withdrawal among female participants, and this early onset of changes in pain perception among female participants led to a longer duration of altered pain perception [37]. Furthermore, Cosgrove demonstrated an even more significant reduction in pain perception threshold and tolerance after 7–13 days of smoking cessation [39].

Gender

The effect of nicotine on pain differs by gender. A recent review showed that nicotine generally has an analgesic effect among males but not among female participants [31]. However, whether the changes in pain perception during withdrawal vary by gender is not known. Eight of 13 studies in this review either did not report additional information on gender-specific differences [3, 17, 39, 40], or similar changes in pain perception were observed among males and females [38, 42, 43]. Four studies included only male or female participants; therefore, no conclusions could be drawn from these studies on gender-specific changes in pain perception [34, 41, 45, 46]. In the remaining two studies, both reported higher pain tolerance among male participants than female participants in the pain tests [37, 47]. Additionally, Bagot showed a change in pain perception among males after performing the cold pressor test, while female smokers showed no change during the study [37].

Postoperative Pain

Postoperative pain was the most frequently studied acute pain condition: six studies reported postoperative pain assessments and opioid requirements [34, 40, 41, 44–46], five investigated the need for analgesic medication [34, 38, 40, 41, 46], and five reported pain intensity [17, 33, 39, 42, 45]. One study involved pulmonary resection [46], one involved laparoscopic gastrectomy [41], one involved liver resection [45], one involved

Table 3 Studies in the postoperative setting

Author (year)	Type of surgery	Type of anesthesia	Pain management	Pain assessment tool	Outcome on opioid consumption	Pain outcomes
Woodside (2000)	Gynecological pelvic surgery	n.r.	n.r.	n.r.	n.r.	Never-smokers had significantly lower opioid demand than ex-smokers or current smokers
Creekmore (2004)	Coronary artery bypass graft	n.r.	Mostly PCA (fentanyl)	n.r.	Smoking cessation resulted in a 33% higher opioid requirement in the first 48 h compared with nonsmokers	n.r
Shen (2017)	Hepatic resection	TIVA	PCA (sufentanil)	VAS	Smokers required more opioid postoperatively	The VAS scores at the various timepoints (6 h, 24 h, and 48 h but not 1 h after surgery) were clearly higher in the abstinent smoking group than the nonsmoking group
Zhao (2018)	Thoracoscopic radical resection of lung cancer	TIVA and sevoflurane, remifentanil	PCA (sufentanil)	VAS	Ex-smokers required more sufentanil at all timepoints (6, 12, 24, and 48 h postoperatively) than nonsmokers	Ex-smokers had higher pain scores both at rest and during cough at all timepoints than non-smokers Patients who discontinued smoking < 3 weeks before surgery had the highest pain scores at each timepoint
Kim (2021)	Laparoscopic distal gastrectomy with gastroduodenostomy	TIVA	PCA (oxycodone)	NRS	As the duration of smoking cessation increased, the amount of postoperative opioid requirements decreased	On POD 0, the NRS score in patients who had ceased smoking within 1 month of surgery, was significantly higher than that in non-smokers or smokers who had ceased smoking more than 1 month before surgery

coronary artery bypass grafting [40], one pelvic/gynecological surgeries (cesarean section, vaginal, and abdominal hysterectomies) [34, 41], and one study involved scheduled noncardiac surgery [44]. These studies corroborated our hypothesis that there is an increased postoperative need for opioids after nicotine withdrawal. In addition, all six publications demonstrated a significantly higher need for analgesics among abstinent smokers.

It is worthwhile noting that two [40, 45] of these six studies compared abstinent smokers only with nonsmokers. However, nonsmokers tended to need less pain medication overall than smokers. Another two studies [41, 46] compared the effect of smoking cessation intervals of different lengths. Zhao showed that participants needed more opioids after 3 weeks of abstinence or shorter than smokers with longer than 3 weeks of abstinence [46]. Kim showed that postoperative opioid requirement decreased with increased duration of smoking cessation among patients who received fentanyl (1 µg/kg) or oxycodone (0.1 mg/kg) 30 min before the end of the surgery with postoperative intravenous patient-controlled analgesia comprising oxycodone and rescue analgesics such as ketorolac (30 mg), tramadol (50 mg), and meperidine (30 mg) [41]. Although clinical practice guidelines recommend a minimum of 8 weeks of smoking abstinence before surgery to reduce perioperative complications and smoking remission rates, this recommendation is not specific to the effects on postoperative pain [48].

Future Direction

Future studies should investigate whether an adapted pain therapy can positively influence smoking cessation. For example, Nakajima showed that smokers who perceive pain more before withdrawal have a higher risk of relapse [47]. They concluded that assessment of pain perception (e.g., by cold pressor test) could be used to identify smokers at increased risk of relapse. Furthermore, Powers concluded in their study that prolonged pain might lead to increased nicotine use, and it will be essential to

Table 3 continued

Author (year)	Type of surgery	Type of anesthesia	Pain management	Pain assessment tool	Outcome on opioid consumption	Pain outcomes
Nazir (2021)	Elective noncardiac surgery	GA	Intravenous tramadol	VAS	n.r.	The RR of mild to moderate pain in patients who stopped smoking for 48 h at PACU and 3 h postoperatively was 3.60 and 3.90, respectively, and these are statistically significant as compared with the patients with duration of cessation of more than 4 weeks

GA general anesthesia, *NRS* numeric rating scale, *PACU* post-anesthesia recovery unit, *POD* postoperative day, *n.r.* not reported, *TIVA* total intravenous anesthesia, *VAS* visual analog scale

investigate the benefits of pharmacotherapy to improve the control of these symptoms [49].

Likewise, it should be considered how to manage smoking cessation before elective acute pain exposures, i.e., surgery or other painful interventions. More studies on the optimal timing should be conducted.

CONCLUSION

Most studies examined in this systematic review show a negative influence of smoking cessation on acute pain. In addition, short-term preoperative nicotine withdrawal negatively impacts postoperative pain and postoperative opioid requirements. The currently available evidence, however, is insufficient to draw firm conclusions on the affected pain modalities, the duration of the altered pain perception, and whether male and female smokers are equally affected due to both quality (high heterogeneity) and quantity (scarcity of research in the smoking cessation pain domain) of available studies.

Our results warrant increased attention and care for pain management among patients in the acute phase of nicotine withdrawal.

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