

Effect of perioperative high-dose transdermal nicotine patch on pain sensitivity among male abstinent tobacco smokers undergoing abdominal surgery: A randomized controlled pilot study

Chengcheng Zhu¹ | Yanzhi Bi^{2,3} | Kai Wei¹ | Kunming Tao¹ | Li Hu^{2,3} | Zhijie Lu¹ 

¹Department of Anesthesiology, Shanghai Eastern Hepatobiliary Surgery Hospital, Shanghai, China

²CAS Key Laboratory of Mental Health, Institute of Psychology, Beijing, China

³Department of Psychology, University of Chinese Academy of Sciences, Beijing, China

Correspondence

Kunming Tao and Zhijie Lu, Department of Anesthesiology, Shanghai Eastern Hepatobiliary Surgery Hospital, Shanghai, China.

Email: kunmingtao@yeah.net and lzjwxyz@163.com

Li Hu, Key Laboratory of Mental Health, Institute of Psychology, Chinese Academy of Sciences, Beijing, China.

Email: huli@psych.ac.cn

Funding information

Shanghai Municipal Science and Technology Commission, Grant/Award Number: 17411960400; National Natural Science Foundation of China, Grant/Award Numbers: 31800926, 31822025, 32071061; Shanghai Hospital Development Center, Grant/Award Number: SHDC12018X19

Abstract

Background and Aims: Previous studies have focused on the role of perioperative nicotine replacement therapy (NRT) in improving the success rate of long-term smoking cessation in tobacco smokers. This study aimed to measure the effectiveness of high-dose NRT in alleviating postoperative pain for male abstinent smokers receiving abdominal surgery.

Design: This was a parallel-group, randomized, double-blind and controlled pilot trial.

Setting and participants: In total, 101 male smoking-abstinent patients from the Eastern Hepatobiliary Surgery Hospital, Shanghai, China, from 8 October 2018 to 10 December 2021.

Interventions: Patients started smoking cessation on admission to the hospital ward. Patients received 24-hour transdermal nicotine patches ($n = 50$) or placebo ($n = 51$) every day from admission until 48 hours after surgery.

Measurements: The primary outcomes were pre-surgery pain thresholds and total consumption of analgesics within the first 48 hours after surgery. Secondary outcomes included postoperative pain and sedation scores, nausea, vomiting and fever frequency within the treatment period.

Findings: Both pre-surgery electrical and mechanical pain thresholds in the NRT group were higher than those in the placebo group ($P = 0.004$ and $P = 0.020$, respectively). The 48-hour postoperative analgesic consumption was significantly lower for smoking-abstinent patients receiving NRT than those receiving placebo (standardized morphine equivalent requirement, median [interquartile range], 1.80 [1.47, 2.32] mg/kg vs 2.22 [1.62, 2.82] mg/kg, $P = 0.011$). Postoperative pain intensity was significantly lower in the NRT group than that in the placebo group at 1st hour and 24th hour post-surgery ($P < 0.001$ and $P = 0.012$, respectively). The incidence of treatment-related adverse events was not significantly different between groups.

Conclusions: Perioperative high-dose nicotine replacement therapy may help to relieve postoperative pain among male smoking-abstinent patients undergoing abdominal surgery.

KEYWORDS

abdominal surgery, male smoker, nicotine replacement therapy, nicotine withdrawal, pain sensitivity, postoperative pain

INTRODUCTION

There are ~1.4 billion tobacco smokers worldwide [1]. Smoking is a public health problem that increases surgical patients' risk of in-hospital mortality by 20% and that of major complications by 40% [2]. The perioperative period is considered to be the best time to initiate a smoking cessation program, and these programs should be recommended before surgery [3]. In contrast to developed countries, many developing countries have not established a sound surgery appointment system, and smokers are often unable to participate in a standard preoperative smoking cessation program. Therefore, most patients undergo surgery while experiencing acute nicotine withdrawal. For this reason, many clinical studies have explored smoking cessation plans starting at patient admission [4].

One concern regarding sudden smoking abstinence is nicotine withdrawal-associated hyperalgesia. Clinical study results have suggested that nicotinic acetylcholine receptor (nAChR) availability during smoking abstinence is positively correlated with experimental pain ratings, and nicotine withdrawal-associated hyperalgesia emerges within the first few hours of smoking abstinence [5]. This may present challenges to perioperative pain management in smokers. Nicotine replenishment can neutralize the consequences of a sudden increase in unbound nAChR ligands caused by nicotine withdrawal. Therefore, nicotine replacement therapy (NRT) is recommended to relieve postoperative pain in smokers [6]. Paradoxically, a single nicotine patch with a dose of 5 to 15 mg failed to affect postoperative pain scores in abstinent smokers in one study [7]. This suggests that a unified or low dose of NRT may limit the effect in alleviating nicotine withdrawal-associated hyperalgesia because individual nicotine exposure varies among smokers. Some studies have investigated the starting NRT dose for heavy smokers during hospitalization, but the potential impact of high-dose NRT on perioperative pain outcomes has not been examined in these studies [8].

We conducted a pilot study among male smoking-abstinent patients who received short-term nicotine patch doses of 21 or 42 mg/day based on their daily nicotine exposure levels. The primary goal was to test the effects of intensive perioperative NRT on pain thresholds and 48-hour postoperative analgesic consumption among male smokers. The secondary goal was to examine the effects of the nicotine patch on postoperative pain scores, sedation, postoperative nausea and vomiting and fever perioperatively.

METHODS

Study participants

We screened patients who were scheduled to undergo abdominal surgery. We included smokers who met criteria for nicotine

dependence of the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-V), smoked more than 10 cigarettes per day in the past 6 months and had no successful smoking abstinence over 1 month [9]. The exclusion criteria are listed in the Supporting information. This study was approved by the Ethics Committee of Medical Research at Eastern Hepatobiliary Surgery Hospital and written informed consent was obtained from all enrolled patients.

Study design and procedure

Patients began smoking cessation on admission to the hospital ward. Using an independent planner's computer-generated code, abstinent patients were randomly assigned to either the NRT group or the placebo group (Figure 1). Patients assigned to the NRT group received 24-hour transdermal nicotine patches (SanJods) every day from the admission day until 48 hours after surgery. Nicotine patches were provided in a sealed opaque envelope. Patches were placed on bare skin in different areas away from the surgical site and were replaced daily. The 21 mg, 42 mg and placebo patches were identical in appearance and weight. All participants wore one patch every day.

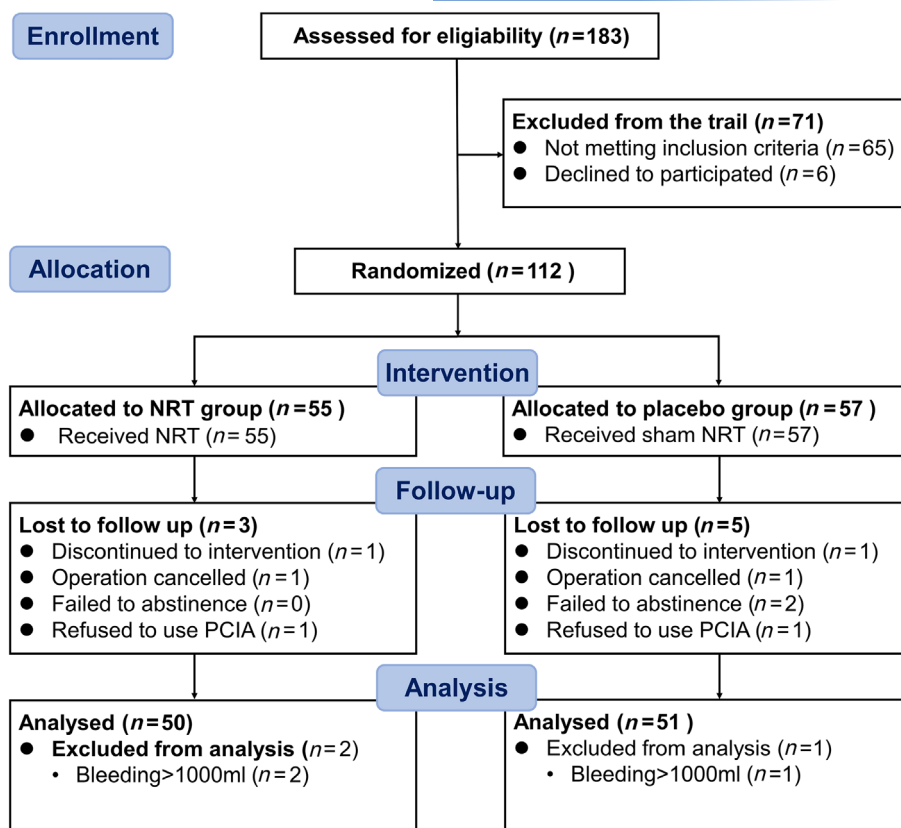
Nicotine patch doses were determined according to the daily number of cigarettes smoked by each patient before admission. Patients who smoked ≤ 20 cigarettes per day received a dose of 21 mg/day; patients who smoked > 20 cigarettes per day received a dose of 42 mg/day [10]. The patients, surgical team and clinical inter-viewers were blinded to the group assignments. If a patient had severe postoperative complications, the planner could unblind the group assignment. Details of anesthesia delivery and perioperative pain control are listed in the Supporting information.

Outcomes

At enrollment, the Fagerström Test for Nicotine Dependence, Minnesota Nicotine Withdrawal Scale (MNWS) and Brief Questionnaire of Smoking Urges were used to assess participants' nicotine dependence and withdrawal.

The primary outcomes were the pre-surgery pain thresholds and total consumption of analgesics within the first 48 hours after surgery. Pain thresholds were evaluated using an electrical stimulator and von Frey filaments before anesthesia induction (details in the Supporting information). Analgesic doses were first converted to morphine equivalent dosing using previously reported conversions [11]. Doses were then standardized for body weight to obtain the standardized morphine equivalent requirement (SMER, mg/kg). Postoperative pain scores were evaluated using a numerical rating scale

FIGURE 1 Flow of patients in the study.



(0 to 10), with 0 being 'no pain' and 10 being 'the worst pain imaginable.'

Secondary outcomes included the following: (i) postoperative pain scores, (ii) nausea and vomiting frequency, (iii) Ramsay sedation score, and (iv) fever frequency within the treatment period.

Statistical analysis

On the basis of the preliminary test results for 48-hour analgesic consumption for 15 patients in each group, a sample size of 92 patients (46 patients per group) would provide a power of $(1 - \beta) = 0.90$ to detect a between-group difference, assuming a two-sided significance level at $\alpha = 0.05$. The mean values and standard deviation of SMER in each group (NRT: 1.86 mg/kg, 0.9; sham: 2.55 mg/kg, 1.15) were calculated using G*power software (version 3.1.9.7).

For primary and secondary outcomes, the Mann-Whitney test was used for data with a non-normally distribution (SMER, pain thresholds and Ramsay sedation score). For categorical variables, the χ^2 and Fisher's exact tests were used. To test whether NRT affects the perceived intensity of postoperative pain within 48 hours after surgery, we performed a two-way mixed-design analysis of variance (ANOVA) with a between-subject factor ('group': NRT and placebo) and a within-subject factor ('postoperative time': 1st hour, 24th hour and 48th hour) on postoperative pain scores. When the interaction between the two factors was significant, *post*

hoc tests were performed. All statistical analyses were performed in SPSS 17.0 (SPSS), and the statistical significance level was set at 0.05.

RESULTS

As shown in Figure 1, a total of 112 adult male smokers were randomized and 101 participants were included in the final analysis. There were no missing data among participants recruited to the study. All patients enrolled in this study underwent partial hepatectomy and were in American Society of Anesthesiologists classes I–II. Baseline demographic characteristics, blood indices, surgical details and smoking behaviors were comparable between the two groups (Table 1).

The total nicotine dose received by participants in the NRT group was 164.64 ± 66.73 mg, with a median treatment time of 7 days (interquartile range, [5, 9]). Compared with the admission day, the expired carbon monoxide concentrations in both groups were significantly decreased on the surgery day ($P < 0.001$ and $P < 0.001$, respectively) (Table 1). Plasma cotinine levels and MNWS scores were significantly different between the groups on the surgery day (Table 1). These results suggest that the included patients were in a smoking-abstinent state during hospitalization, and the cotinine plasma level was effectively supplied by the nicotine patch.

Both pre-surgery electrical and mechanical pain thresholds were higher in the NRT group than those in the placebo group (Table 1). In the NRT group, 48-hour postoperative analgesic consumption (SMER)

TABLE 1 Participant baseline characteristics by study group.

Variables	NRT group (n = 50)	Placebo group (n = 51)
Age, years	56 (48, 62)	54 (48, 66)
Body mass index, kg/m ²	23.62 (0.35)	24.56 (0.36)
Red blood cell, ×10 ¹² /L	4.56 (0.07)	4.60 (0.07)
White blood cell, ×10 ¹² /L	5.71 (4.66, 6.89)	5.30 (4.68, 6.30)
Platelet, ×10 ⁹ /L	164.46 (8.56)	165.94 (9.16)
Hemoglobin, g/L	140.04 (1.70)	140.86 (2.30)
Total bilirubin, µmol/L	13.35 (9.58, 16.55)	12.10 (10.20, 16.60)
Albumin, g/L	41.74 (0.46)	42.67 (0.40)
Alanine transaminase, U/L	31.5 (21.0, 43.75)	26.0 (19.0, 47.0)
Glutamic oxaloacetylase, U/L	27.5 (19.0, 40.25)	26.0 (21.0, 36.0)
Creatinine, µmol/L	78.14 (1.76)	79.33 (1.72)
Duration of surgery, min	118 (90, 156)	115 (90, 155)
Amount of bleeding, mL	200 (200, 300)	200 (200, 400)
Postoperative hospital stays, days	9 (7, 10)	8 (8,10)
Smoking-related		
Cigarettes per day ^a , numbers	20 (15, 20)	20 (15, 20)
Duration of smoking ^a , years	31.42 (1.54)	31.57 (1.38)
Exhaled CO ^a , ppm	7 (6, 8)	8 (6, 9)
FTND ^a	6 (4, 7)	5 (4, 7)
QSU-Brief ^a	26 (18, 34)	25 (19, 35)
Plasma cotinine level ^a , ng/mL	116.7 (4.47)	109.3 (4.04)
Plasma cotinine level ^b , ng/mL	122.5 (3.48)	11.3 (3.06)***
MNWS ^a	3 (2, 5)	4 (3, 5)
MNWS ^b	3 (2, 4)	4 (3, 5)*
Patches used pre-surgery, patches	5 (3, 7)	5 (4, 7)

Data with a normally distribution are presented as mean (standard error of the mean) and data with a non-normally distribution are presented as median (interquartile range).

Abbreviations: CO, carbon monoxide; FTND, Fagerström Test for Nicotine Dependence; MNWS, Minnesota Nicotine Withdrawal Scale; NRT, nicotine replacement therapy; QSU-Brief, Brief Questionnaire of Smoking Urges.

^aThese indicators were measured on the day of admission.

^bThese indicators were measured on the day of surgery.

* $P < 0.05$; *** $P < 0.001$.

was significantly lower than that in the placebo group (median [interquartile range], 1.80 [1.47, 2.31] mg/kg vs 2.22 [1.62, 2.82] mg/kg, $P = 0.011$) (Table 2). For postoperative pain within the first 48 hours, two-way mixed-design ANOVA showed significant main effects of 'time' ($F [2, 99] = 73.14$, $P < 0.001$, partial $\eta^2 = 0.43$) and 'group' ($F [1, 99] = 11.54$, $P = 0.001$, partial $\eta^2 = 0.104$) and a significant interaction between the two factors ($F [2, 99] = 8.54$, $P < 0.001$, partial $\eta^2 = 0.08$). Post hoc tests showed that postoperative pain was significantly lower in the NRT group than that in the placebo group at 1st hour and 24th hour post-surgery (Table 2).

No significant differences were noted between the groups for sedation scores, nausea, vomiting and fever rates within the treatment period (Table 2). There were no severe complications among the participants.

DISCUSSION

In this pilot clinical trial, we found that a perioperative NRT at a dose of 21 to 42 mg/day helped to reduce pain sensitivity in male smoking-abstinent patients. This NRT dose also led to a 0.42 mg/kg median reduction in 48-hour postoperative analgesic consumption (SMER) in these patients. Consistent with previous reports, the nicotine patch doses in our study were well tolerated, and we did not observe a notable increase in adverse events with high-dose transdermal nicotine patches.

Accumulating evidence indicates that pain and nicotine use interact in a reciprocal manner to influence their respective trajectories and outcomes [12]. Nicotine-deprived smokers demonstrate greater sensitivity to laboratory pain than both non-smokers and non-

TABLE 2 Treatment effect of nicotine patch on primary and secondary outcomes in male smoking-abstinent patients.

Variables	NRT group (n = 50)	Placebo group (n = 51)
Electrical pain threshold (mA)	1.32 (1.17, 1.68)	1.17 (0.95, 1.54)*
Mechanical pain threshold (g)	11.02 (3.86, 30.96)	5.1 (2.0, 11.06)*
48 h SMER (mg/kg)	1.8 (1.47, 2.31)	2.22 (1.62, 2.82)*
Postoperative pain intensity ratings		
1st hour	3.04 (0.17)	4.16 (0.20)***
24th hour	3.40 (0.14)	3.96 (0.14)*
48th hour	3.40 (0.12)	3.88 (0.15)*
Nausea and vomiting, numbers	7	9
Fever, numbers	11	14
The Ramsay sedation score ^a	2 (2, 2)	2 (2, 2)

Data with a normally distribution are presented as mean (standard error of the mean) and data with a non-normally distribution are presented as median (interquartile range).

Abbreviations: NRT, nicotine replacement therapy. SMER, standardized morphine equivalent requirement.

^aThe sedation score was evaluated at 1 hour, 24 hours and 48 hours after surgery using the Ramsay sedation scale. The results presented are the highest postoperative score in each group.

* $P < 0.05$; *** $P < 0.001$.

deprived smokers, and this increased pain sensitivity during the initial phases of smoking cessation may precipitate relapse [12]. As for the neurobiological mechanism of nicotine withdrawal-induced hyperalgesia, nicotine withdrawal reportedly causes a sudden increase in unbound nAChR ligands, which decreases the central release of opioids, norepinephrine and serotonin [13]. The decrease in these neurotransmitters further leads to descending pain modulation system dysfunction, which contributes to the adverse effects of analgesics in smokers [14]. Therefore, NRT should be an important part of both the perioperative smoking cessation plan and postoperative multimodal analgesia for abstinent smokers.

Currently, the effects of nicotine on postoperative pain are mixed in both smokers and non-smokers. In 2004, Flood et al. [15] first found that treatment with a single 3-mg dose of nicotine immediately before emergence from anesthesia was associated with lower reported pain scores during the first day after surgery in female non-smokers. Since then, eight clinical trials have been conducted to assess the analgesic efficacy of nicotine in surgical patients, showing that nicotine can reduce postoperative pain scores from the first hour after surgery to the following 5 days [16, 17]. Unfortunately, seven of these studies excluded smokers, and only one study enrolled abstinent smokers. In this small-sample trial, the authors found that a single 5 to 15-mg dose of nicotine in a patch before anesthesia induction failed to relieve postoperative pain or reduce opioid use in smoking-abstinent participants [7].

In our analysis of these studies, we found that most were conducted among female non-smokers, and nicotine supplement doses ranged from 3 to 17 mg. These doses are consistent with the tobacco use and dependence guidelines, which recommend an initial transdermal nicotine replacement dose of 22 mg daily for individuals who smoke 10 or more cigarettes per day [10]. However, the 22-mg patch was shown to replace only approximately half of the baseline

serum nicotine and cotinine levels in these smokers [10]. Therefore, higher nicotine patch doses may be needed in acute abstinent smokers to test the efficacy of NRT on nicotine withdrawal-associated pain sensitivity changes. Consistent with this hypothesis, here, we report that the demand for analgesics was reduced in smoking-abstinent patients when nicotine was replenished in an amount equal to their regular smoking exposure. Even with fewer opioid analgesics, postoperative pain in the 48 hours after surgery was significantly lower for smokers with NRT in our study than for those with placebo.

This study had some limitations. First, only male heavy regular smokers were included in this study; this may limit the generalizability of our findings to lighter or intermittent smokers. Second, some potential side effects of using the nicotine patch were not detected because the present study was not designed to provide adequate statistical power for this analysis. Third, we only explored the efficacy and safety of perioperative use of a high-dose nicotine patch on pain management. The guidelines indicate that the purpose of perioperative NRT is to improve the success rate of long-term smoking cessation and prevent relapse [18]. Fourth, the duration of patch treatment varied in our study (a short-term range, 4–14 days), which may reduce the rigor in the experimental design.

CONCLUSIONS

Our study provides initial evidence that smokers may experience increased sensitivity to acute pain during the early stages of smoking abstinence. This may be especially important for the large population of smokers who undergo painful surgical treatment. A perioperative nicotine patch at a dose of 21 to 42 mg could effectively relieve postoperative pain in male smoking-abstinent patients undergoing

abdominal surgery. In future studies, increasing the initial perioperative NRT dose for heavy smokers should be considered.

AUTHOR CONTRIBUTIONS

Chengcheng Zhu: Data curation (equal); formal analysis (equal); investigation (lead); resources (equal); software (equal); validation (equal); visualization (equal); writing—original draft (equal); writing—review and editing (equal). **Yanzhi Bi:** Data curation (equal); formal analysis (equal); methodology (equal); resources (equal); software (equal); validation (equal); visualization (equal); writing—original draft (equal); writing—review and editing (equal). **Kai Wei:** Data curation (supporting); formal analysis (supporting); investigation (supporting); methodology (equal); resources (equal); software (supporting); validation (supporting); visualization (supporting). **Kunming Tao:** Data curation (equal); formal analysis (equal); funding acquisition (equal); supervision (equal); visualization (equal); writing—original draft (equal); writing—review and editing (equal). **Li Hu:** Conceptualization (equal); funding acquisition (equal); methodology (equal); project administration (equal); resources (equal); supervision (equal); visualization (equal); writing—review and editing (equal). **Zhijie Lu:** Conceptualization (equal); funding acquisition (equal); methodology (equal); project administration (equal); resources; supervision (equal).

ACKNOWLEDGEMENTS

We thank Jodi Smith, PhD, ELS, from Liwen Bianji (Edanz) (www.liwenbianji.cn) for editing the English text of a draft of this manuscript.

DECLARATION OF INTERESTS

None.

CLINICAL TRIAL REGISTRATION DETAILS

All procedures followed were in accordance with the ethical standards of the Responsible Committee on Human Experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2000. The experiment was approved by the ethics committee of the Eastern Hepatobiliary Surgery Hospital. The experiment was registered in the Chinese Clinical Trial Registry as ChiCTR-IOR-17013591 (www.chictr.org.cn/showprojEN.html?proj=23186).

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

ORCID

Zhijie Lu  <https://orcid.org/0000-0002-0561-0591>

REFERENCES

- Creedon TB, Wayne GF, Progovac AM, Levy DE, Cook BL. Trends in cigarette use and health insurance coverage among US adults with mental health and substance use disorders. *Addiction*. 2023;118(2):353–364. <https://doi.org/10.1111/add.16052>
- Pierre S, Rivera C, Le Maître B, Ruppert AM, Bouaziz H, Wirth N, et al. Guidelines on smoking management during the perioperative period. *Anaesth Crit Care Pain Med*. 2017;36(3):195–200. <https://doi.org/10.1016/j.accpm.2017.02.002>
- Fankhauser CD, Affentranger A, Cortonesi B, Jeker U, Gass M, Minervini F, et al. Preoperative smoking cessation program in patients undergoing intermediate to high-risk surgery: a randomized, single-blinded, controlled, superiority trial. *Trials*. 2022;23(1):717. <https://doi.org/10.1186/s13063-022-06628-8>
- Hartmann-Boyce J, Chepkin SC, Ye W, Bullen C, Lancaster T. Nicotine replacement therapy versus control for smoking cessation. *Cochrane Database Syst Rev*. 2018;5(1):Cd000146. <https://doi.org/10.1002/14651858.CD000146.pub5>
- Ditre JW, Zale EL, LaRowe LR, Kosiba JD, De Vita MJ. Nicotine deprivation increases pain intensity, neurogenic inflammation, and mechanical hyperalgesia among daily tobacco smokers. *J Abnorm Psychol*. 2018;127(6):578–589. <https://doi.org/10.1037/abn0000353>
- Shen L, Wei K, Chen Q, Qiu H, Tao Y, Yao Q, et al. Decreased pain tolerance before surgery and increased postoperative narcotic requirements in abstinent tobacco smokers. *Addict Behav*. 2018;78:9–14. <https://doi.org/10.1016/j.addbeh.2017.10.024>
- Olson LC, Hong D, Conell-Price JS, Cheng S, Flood P. A transdermal nicotine patch is not effective for postoperative pain management in smokers: a pilot dose-ranging study. *Anesth Analg*. 2009;109(6):1987–1991. <https://doi.org/10.1213/ANE.0b013e3181bd1612>
- Mishriky BM, Habib AS. Nicotine for postoperative analgesia: a systematic review and meta-analysis. *Anesth Analg*. 2014;119(2):268–275. <https://doi.org/10.1213/ANE.0b013e3182a8fa7b>
- Bi Y, Zhang Y, Li Y, Yu D, Yuan K, Tian J. 12h abstinence-induced right anterior insula network pattern changes in young smokers. *Drug Alcohol Depend*. 2017;176:162–168. <https://doi.org/10.1016/j.drugalcdep.2017.02.019>
- Lindson N, Chepkin SC, Ye W, Fanshawe TR, Bullen C, Hartmann-Boyce J. Different doses, durations and modes of delivery of nicotine replacement therapy for smoking cessation. *Cochrane Database Syst Rev*. 2019;4(4):Cd013308. <https://doi.org/10.1002/14651858.CD013308>
- Qiu Q, Choi SW, Wong SS, Irwin MG, Cheung CW. Effects of intraoperative maintenance of general anaesthesia with propofol on postoperative pain outcomes - a systematic review and meta-analysis. *Anaesthesia*. 2016;71(10):1222–1233. <https://doi.org/10.1111/anae.13578>
- LaRowe LR, Ditte JW. Pain, nicotine, and tobacco smoking: current state of the science. *Pain*. 2020;161(8):1688–1693. <https://doi.org/10.1097/j.pain.0000000000001874>
- Millan MJ. Descending control of pain. *Prog Neurobiol*. 2002;66(6):355–474. [https://doi.org/10.1016/S0301-0082\(02\)00009-6](https://doi.org/10.1016/S0301-0082(02)00009-6)
- Shen L, Qiu HB, Xu HH, Wei K, Zhao L, Zhu CC, et al. Nicotine withdrawal induces hyperalgesia via downregulation of descending serotonergic pathway in the nucleus raphe magnus. *Neuropharmacology*. 2021;189:108515. <https://doi.org/10.1016/j.neuropharm.2021.108515>
- Flood P, Daniel D. Intranasal nicotine for postoperative pain treatment. *Anesthesiology*. 2004;101(6):1417–1421. <https://doi.org/10.1097/0000542-200412000-00023>
- Matthews AM, Fu R, Dana T, Chou R. Intranasal or transdermal nicotine for the treatment of postoperative pain. *Cochrane Database Syst Rev*. 2016;2016(1):Cd009634. <https://doi.org/10.1002/14651858.CD009634.pub2>
- Hong D, Conell-Price J, Cheng S, Flood P. Transdermal nicotine patch for postoperative pain management: a pilot dose-ranging study. *Anesth Analg*. 2008;107(3):1005–1010. <https://doi.org/10.1213/ane.0b013e318163204f>

18. Przulj D, Wehbe L, McRobbie H, Hajek P. Progressive nicotine patch dosing prior to quitting smoking: feasibility, safety and effects during the pre-quit and post-quit periods. *Addiction*. 2019;114(3):515–522. <https://doi.org/10.1111/add.14483>

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Zhu C, Bi Y, Wei K, Tao K, Hu L, Lu Z. Effect of perioperative high-dose transdermal nicotine patch on pain sensitivity among male abstinent tobacco smokers undergoing abdominal surgery: A randomized controlled pilot study. *Addiction*. 2023. <https://doi.org/10.1111/add.16224>