J Anesth (2013) 27:569–574
DOI 10.1007/s00540-013-1565-0

ORIGINAL ARTICLE

The effects of secondhand smoke on postoperative pain and fentanyl consumption

Mustafa Said Aydogan · Erdogan Ozturk · Mehmet Ali Erdogan · Aytac Yucel · Mahmut Durmus · Mehmet Ozcan Ersoy · Cemil Colak

Received: 13 November 2012 / Accepted: 21 January 2013 / Published online: 9 February 2013

Abstract
Background Although the need for increased postoperative analgesia in smokers has been described, the effect of secondhand smoke on postoperative analgesia requirements has not been studied. We examined the effects of secondhand smoke on fentanyl consumption and postoperative pain.
Methods In this study, 101 patients (American Society of Anesthesiology physical status I and II) who underwent abdominal hysterectomy were divided into 3 groups according to history of exposure to cigarette smoke as per medical records which was retrospectively confirmed by measurement of serum cotinine: smokers ($n = 28$), nonsmokers ($n = 31$), and secondhand smokers ($n = 32$). All patients received propofol–remifentanil total intravenous anesthesia and used fentanyl patient controlled analgesia for postoperative pain. The fentanyl consumption visual analogue scale-pain intensity (VAS-PI) score and side effects were recorded in the postanesthesia care unit (PACU) and at 2, 4, 6, and 24 h after surgery.
Results Fentanyl consumption at all the evaluation time points was significantly higher in secondhand smokers than in nonsmokers ($P < 0.05$). However, fentanyl consumption in secondhand smokers was lower than that in smokers in the PACU and at 24 h ($P < 0.05$). VAS-PI scores during movement and at rest in the PACU and at 4, 6, and 24 h after surgery were higher in secondhand smokers than in nonsmokers ($P < 0.05$). There were no statistically significant differences between the groups with regard to side effects such as nausea, vomiting, and dizziness ($P > 0.05$).
Conclusion Secondhand smoking was associated with increased postoperative fentanyl consumption, and increased VAS-PI scores. These findings may be beneficial for managing postoperative pain in secondhand smokers.

Keywords Secondhand smoke · Fentanyl consumption · Pain · Postoperative

Introduction

Pain is one of the most common symptoms causing patient discomfort during the early postoperative period [1]. Postoperative pain is a problem in many patients, and treatment with high doses of opiates is often associated with adverse effects, including nausea [2]. Daily smoking is a strong and independent risk factor for increased postoperative opioid use [3–5]. Approximately, 1 of 10 nonsmokers is exposed to secondhand smoke (SHS) at home [6]. Despite the large numbers of secondhand smokers undergoing surgery, the current reports examining the association between smoking and increased postoperative opioid use only include smokers and do not address SHS [7].

Accurate estimation of exposure to SHS is required for the meaningful study of its effects. Because of the deleterious effects of smoking on general health, patients are now questioned before surgery to determine their smoking

M. S. Aydogan (✉) · M. A. Erdogan · A. Yucel · M. Durmus · M. O. Ersoy
Department of Anesthesiology and Reanimation, Inonu University, Faculty of Medicine, Malatya, Turkey
e-mail: dr_mustafasaid@hotmail.com

E. Ozturk
Department of Anesthesiology and Reanimation, Bezm-i Alem University, Faculty of Medicine, Istanbul, Turkey

C. Colak
Department of Biostatistics and Medical Informatics, Inonu University, Faculty of Medicine, Malatya, Turkey

habits. However, responses to self-reported smoking questionnaires are often inaccurate; the misrepresentation rate ranges from 2 to 50 % [8]. Unfortunately, there are no means by which serum nicotine concentrations can be accurately and reliably measured beyond several hours after smoking because the half-life of nicotine is only 0.05–2 h [9]. However, nicotine is hepatically metabolized to cotinine by the cytochrome P450 system in a 2-step process (CYP2A6 and aldehyde oxidase). The half-life of cotinine is 18–24 h, which makes it a more reliable marker of recent nicotine exposure [10]. A serum cotinine concentration of >50 ng/ml represents active smoking, and an intermediate cotinine concentration (10–50 ng/ml) represents either very recent quitting or SHS [11–13].

To our knowledge, no prospective, controlled clinical studies have been conducted to determine whether SHS exposure affects postoperative pain and opioid use. The aim of this study was to investigate the effects of SHS on pain and opioid use during the early postoperative period in women undergoing gynecological surgery.

Materials and methods

After approval by the Ethics Committee of the Inonu University Turgut Ozal Medical Centre (Ethical Committee Nr. 2008/02, 02 January 2008, President: A Kafkaslı), Malatya, Turkey, an observational study was prospectively undertaken and included eligible consecutive female patients scheduled to undergo elective total abdominal hysterectomy (TAH) ($n = 101$, American Society of Anesthesiologists physical status I and II; age range, 25–65 years; BMI, <35 kg/m^2) under general anesthesia. Written consent was required from all participants in the study. Exclusion criteria included known allergy or contraindication to any of the study medications, pain requiring daily preoperative use of opioids or non-opioid analgesics, known psychiatric disorders, drug or alcohol abuse, refusal to participate, and the performance of a second surgery within 24 h. We also excluded patients who were not able to use the patient controlled analgesia (PCA) device or were unable to understand the visual analogue scale (VAS) of pain. Patients who were smokers, but had not smoked during the last week before surgery were also excluded. According to the history of exposure to cigarette smoke as per medical records, which was retrospectively confirmed by measurement of serum cotinine, the patients were divided into three groups: group S, smokers with high cotinine levels (>50 ng/ml); group NS, nonsmokers with low cotinine levels (1–10 ng/ml); and group SHS, secondhand smokers with intermediate cotinine levels (11–50 ng/ml). SHS exposure was defined according to a previously published algorithm [9, 11–13].

On the day before surgery, each patient donated approximately 3 ml of blood for assessment of preoperative cotinine serum levels. Serum samples were frozen at −80 °C and stored in batches for subsequent analysis. We measured serum cotinine concentrations by using a competitive microplate immunoassay according to the manufacturer's instructions, using the manufacturer's standards for the control dose curve (DRG diagnostics, Marburg, Germany). Cotinine testing was performed using commercially available kits (Cotinine EIA, Florence, Italy).

The same surgeon conducted all of the TAH surgeries using the same surgical method. Consistent with the prevailing standard of care, no analgesics or sedatives were used preoperatively. All patients fasted from midnight of the previous day until the operation. All surgeries began between 08:30 am and 11:30 am. Metoclopramide [20 mg intravenous (iv)] was administered to all patients for antiemetic prophylaxis. Upon arrival in the operating room, noninvasive arterial pressure (BP), electrocardiography, capnography, and peripheral oxygen saturation were monitored. Two intravenous catheters were put in place and 5 ml/kg/min Ringer's lactate solution was infused. A bispectral index (BIS) monitor (A-2000XP host rev 3, 3; Aspect Medical Systems) was used to evaluate the depth of anesthesia. A standardized anesthetic technique was used for all patients, as follows: 30 s after the initiation of 0.5 μg/kg/min remifentanil, a 0.5 mg/kg bolus dose of propofol was administered. An additional bolus dose of 20 mg propofol was administered every 20 s until loss of consciousness (LOC), as defined by loss of reaction to a verbal command. Next, propofol infusion was started at a dose of 75 μg/kg/min. Atracurium 0.6 mg/kg was administered for neuromuscular blockage. The trachea was intubated after the loss of all four twitches to a train-of-four stimulus when the BIS value was between 45 and 60. After intubation, mechanical ventilation was continued with 40 % O_2–air mixture and 35–40 mmHg end-tidal CO_2, and the esophageal temperature probe was placed for body temperature monitoring. At the same time, remifentanil infusion was decreased by 50 %. Anesthesia was maintained with a continuous infusion of 75 μg/kg/min propofol, 0.25 μg/kg/min remifentanil, and 40 % O_2–air mixture. During surgery, maintenance doses of anesthetics were adjusted to maintain mean arterial pressure (MAP) and heart rate (HR) within ±20 % of baseline value and a BIS value of 45–60. Additional atracurium was administered as needed. Fifteen minutes before the anticipated end of the surgical procedure, lornoxicam (8 mg iv) was given; propofol and remifentanil infusions were discontinued after closure of the skin incision. At the end of the surgical procedure, residual neuromuscular blockade was antagonized with iv neostigmine (50 μg/kg) and atropine (20 μg/kg). The trachea was extubated when sufficient spontaneous ventilation (volume-targeted

level >4 ml/kg, respiratory rate >6 breaths/min) and the gag reflex were established. All patients stayed in the hospital for at least 24 h.

Patients were informed that they would receive an opioid analgesic during the postoperative recovery period via the PCA device, but they were not told which drug, dose, or lockout interval would be used. The technique for the PCA device and the VAS-pain intensity (0 = no pain, 10 = worst pain imaginable) analysis were explained to the patients during the preoperative anesthesia consultation. They also received standardized preoperative instructions regarding the use of the PCA device. PCA connected to a venous line was started 30 min before the end of the operation and initiated postoperatively using a commercially available PCA pump (Abbott—APM PompaPain Management Provider® Ireland) in the operating room when the patient first complained of pain. The PCA device, filled with fentanyl (1,500 μg; 70 ml saline) was initially programmed to deliver basal infusion at the rate of 1 ml/h, a bolus of 1 ml, and a lockout time of 10 min. If analgesia was insufficient (VAS-PI > 4), 25 μg rescue fentanyl was given intravenously until the VAS-PI score was <4. Measures were recorded at the post-anesthesia care unit (PACU), and at 2, 4, 6, and 24 h after surgery. To maintain blinding, the VAS-PI score and total amount of postoperative opioids administered were obtained and recorded by an anesthesiologist who did not participate in this study. Overdose of the PCA solution was avoided by closely monitoring the patient's respiratory rate (<12 breaths/min), oxygen saturation (<95 %), and level of consciousness before and after initiating PCA. If nausea and vomiting occurred, 8 mg of ondansetron was administered intravenously.

Endpoint

The primary goal was to determine the amount of fentanyl consumption for 24 h postoperatively. The secondary goal was to determine the VAS-PI score at rest and during movement, and number of patients who experienced side effects (such as respiratory depression, nausea and vomiting, headache, and pruritus).

Statistical analyses

According to post hoc power analysis, for a one-way ANOVA study, sample sizes of 28, 31, and 32 from the 3 groups achieved nearly 100 % power to detect differences between the means versus the alternative of equal means using an F test with a significance level of 0.05. Power analyses were calculated using the PASS software [14]. Values were expressed as mean (SD) or numbers (percentages) as appropriate. To evaluate normality, the Shapiro–Wilk test was performed. The three groups were compared using one-way ANOVA and the post hoc Tukey test was used for homogeneous variances or Tamhane's $T2$ test was used for nonhomogeneous variances in multiple comparisons. Categorical data and postoperative nausea and vomiting (PONV) were analyzed using Pearson's χ^2 test. A P value of <0.05 was considered statistically significant. Statistical analyses were performed by an expert statistician.

Results

One hundred and one patients were considered in the study. Ten patients were excluded from the study for the following reasons: 3 patients refused to participate, 3 patients had psychiatric disorders, 3 patients defined as smokers had not smoked during the last week prior to admission, and 1 patient underwent a second surgery within 24 h. Data from the remaining 91 patients (group S, 28; group NS, 31; group SHS, 32) were analyzed. Demographic characteristics, including age, BMI, duration of anesthesia, duration of surgery, and ASA status, did not differ between the 3 groups of patients (Table 1). Self-reported smoking status and measured serum cotinine concentrations are listed in Table 2.

Table 3 presents a comparison of the results of cumulative fentanyl consumption and pain scores (VAS at rest, VAS during movement) among the 3 groups. Total fentanyl consumption was 594 ± 49 μg in group S, 446 ± 51 μg in group NS, and 534 ± 52 μg in group SHS. Fentanyl consumption at all the evaluation time points was significantly higher in group SHS than in group NS ($P < 0.05$). Similarly, fentanyl consumption was higher at all times in group S than in group NS ($P < 0.05$). Further, fentanyl consumption was higher in the PACU and at 24 h in group S than in group SHS ($P < 0.05$).

Pain scores at rest in the PACU and at 4, 6, and 24 h after surgery were significantly higher in group SHS than in group NS ($P < 0.05$). Similarly, the VAS resting score was higher at all times in group S than in group NS ($P < 0.05$). The VAS resting score was also higher in the PACU and at 24 h in group S than in group SHS ($P < 0.05$). Pain during movement scores were significantly higher at all postoperative times in group SHS than in group NS ($P < 0.05$). Similarly, the VAS movement score was higher at all times in group S than in group NS ($P < 0.05$). The VAS movement score was also higher in the PACU and at 24 h in group S than in group SHS ($P < 0.05$).

There were no significant differences between the groups with regard to postoperative side effects such as nausea, vomiting, and dizziness (Table 4).

Table 1 Patient's demographics and characteristics for surgery and anesthesia

Variable	Group S ($n = 28$)	Group NS ($n = 31$)	Group SHS ($n = 32$)
Age (years)	45.3 ± 6.7	46.6 ± 8.6	43.3 ± 11.4
Duration of surgery (min)	73.3 ± 21.4	67.8 ± 32.1	65.8 ± 23.4
Duration of anesthesia (min)	87.7 ± 20.2	76.6 ± 33.2	80.7 ± 25.7
ASA I/II (*n*)	18/12	19/11	18/12
BMI (kg/m^2)	27 ± 3	26 ± 5	27 ± 1
Rescue analgesic use (%)	3 (17.8)	5 (16.1)	6 (18.5)

Values are mean ± standard deviation (SD) or number and percentage, *n* (%)

Group S smokers, *group NS* nonsmokers, *group SHS* secondhand smokers, *ASA* American Society of Anesthesiologists, *BMI* body mass index

Table 2 Serum cotinine concentration and self-reported smoking status

Serum cotinine concentration level	Self-reported smoking status					
	Group S ($n = 28$)		Group NS ($n = 31$)		Group SHS ($n = 32$)	
	No.	%	No.	%	No.	%
1–10 ng/ml (low)	0	0	30	96.7	1	3.1
11–50 ng/ml (intermediate)	1	3.5	1	3.3	31	96.9
>50 ng/ml (high)	27	96.5	0	0	0	0

The values are number and percentage, *n* (%)

Group S smokers, *group NS* nonsmokers, *group SHS* secondhand smokers

Table 3 Comparison results of the variables with respect to groups

Variable	Group S ($n = 28$)	Group NS ($n = 31$)	Group SHS ($n = 32$)	*P* value[a]
Cumulative fentanyl consumption				
PACU	53.9 ± 7.0	33.3 ± 11.5*,†	41.8 ± 6.7†	<0.001
2 h	82.2 ± 19.7	64.0 ± 19.0*,†	74.5 ± 16.8	0.031
4 h	156.0 ± 27.1	127.5 ± 15.0*,†	141.9 ± 23.5	0.027
6 h	202.7 ± 33.2	164.3 ± 38.9*,†	190.7 ± 33.1	<0.001
24 h	594.1 ± 49.0	446.8 ± 51.8*,†	534.1 ± 52.1†	<0.001
VAS rest				
PACU	3.53 ± 0.5	2.88 ± 0.4*,†	2.83 ± 0.5†	0.042
2 h	3.46 ± 0.3	2.94 ± 0.2†	2.70 ± 0.3	0.006
4 h	2.45 ± 0.3	2.00 ± 0.6*,†	2.43 ± 0.4	0.014
6 h	2.76 ± 0.2	2.20 ± 0.3*,†	2.46 ± 0.3	<0.001
24 h	1.38 ± 0.1	1.11 ± 0.1*,†	1.30 ± .0.2†	<0.001
VAS movement				
PACU	4.88 ± 0.4	3.11 ± 1.5*,†	3.63 ± 0.5†	0.032
2 h	3.94 ± 0.5	2.34 ± 0.8*,†	3.46 ± 0.6	0.023
4 h	2.66 ± 0.9	2.13 ± 0.9*,†	2.38 ± 0.7	<0.001
6 h	2.27 ± 1.2	1.53 ± 1.3*,†	1.96 ± 0.9	0.002
24 h	1.66 ± 0.9	1.26 ± .0.5*,†	1.34 ± 0.9†	<0.001

Values are mean ± standard deviation (SD)

Group S smokers, *group NS* nonsmokers, *group SHS* secondhand smokers, *PACU* postanesthesia care unit, *VAS* visual analogue scale

[a] One-way ANOVA test

* Significantly different compared with group SHS ($P < 0.05$, Tamhane *T*2 test). † Significantly different compared with group S ($P < 0.05$, Tamhane *T*2 test)

Table 4 Adverse events

Variable	Group S ($n = 28$) No.	Group NS ($n = 31$) No.	Group SHS ($n = 32$) No.
PONV	6	7	7
Pruritus	4	4	4
Dizziness	5	6	7
Total	15	17	18

Data are given as number of events

Group S smokers, *group NS* nonsmokers, *group SHS* secondhand smokers, *PONV* postoperative nausea and vomiting, the data are given as numbers

Discussion

The main finding of this study is that secondhand smokers consumed more fentanyl postoperatively and had higher VAS-PI scores than did nonsmokers. To the best of our knowledge, this is the first report to indicate that secondhand smoking is significantly associated with postoperative opioid requirements.

Smoking is known to be an independent risk factor for postoperative opioid use [15]. Creekmore et al. [16] found that smokers deprived of nicotine required more opiates during the first 48 h after coronary artery bypass graft (CABG) than nonsmokers. Woodside [17] retrospectively evaluated the relationship between analgesic use and smoking in 171 women who had undergone pelvic surgery and reported that smokers used approximately 20 % more opiates during the first 12 postoperative hours than did nonsmokers. Stanley et al. [18] showed that after CABG, patients who smoked had increased fentanyl consumption. In the present study, we showed that secondhand smoking also has an effect on the incidence of postoperative pain. Secondhand smokers required a greater amount of fentanyl during the first 24 h after TAH than did nonsmoking patients. Although our findings are similar to those of previous studies, there are several noteworthy methodological differences between the studies. Our study included only women, and the age range of the subjects differed. These factors could affect the results, as the amount of postoperative analgesia required is known to decrease with patient age [19] and women have been shown to have less pain tolerance than men [20].

The physiologic reasons for secondhand smokers requiring more postoperative analgesia are not known. One possible explanation is that a pharmacokinetic interaction occurs between smoking and opiates, particularly if smoking induces the metabolism of opiates. Cigarette smoke may also alter the pharmacokinetics of opioids [21]. Smoking is known to induce the CYP1A2 isoenzyme, thereby increasing the metabolism of some medications [22]. It is also possible that smokers need higher amounts of opiates to control their pain. Exogenously administered opiates and endogenous β-endorphins relieve pain by binding to opioid receptors. A cross-tolerance between exogenous opiates and endogenous opiates, including β-endorphins, has been well demonstrated in animal models [23]. Tolerance to opiates would warrant the administration of higher amounts of opiates postoperatively to control pain. In laboratory animals exposed to nicotine, abstinence enhances nociceptive transmission [24]. Furthermore, symptoms of nicotine abstinence can be attenuated by fentanyl administration in animals [22].

This study has several limitations. First, preoperative nicotine habits were assessed using a questionnaire but were not directly measured. However, we confirmed smoking history by determining cotinine serum levels on the day of surgery. This measurement provided an objective indicator of a patient's smoking habits. Although cotinine concentration has been repeatedly proven to be a reliable indicator of a patient's current smoking habits, this concentration is affected by numerous variables, including the number of cigarettes smoked per day, type of cigarettes smoked (e.g., high-tar vs. low-tar or filtered vs. unfiltered), depth of inhalation, percentage of cigarettes smoked (smoking intensity), individual nicotine metabolism, and cotinine excretion rate. Although self-reported smoking status nearly correlated with cotinine concentration, the level and period of passive smoke exposure is not clear. Second, smoking is associated with a lower incidence of PONV. However, in this study we found no significant differences between the groups with regard to PONV. Total intravenous anesthesia with propofol might be considered 'prophylaxy' for the patients and a prophylactic antiemetic was used as premedication. However, larger studies are required to evaluate the effects of secondhand smoking and confirm these findings.

In conclusion, in addition to smoking, secondhand smoking also increases postoperative pain and the need for opioid analgesics. Compared to a non-smoking status, preoperative secondhand smoking was associated with high postoperative opioid use during the early postoperative course in women undergoing gynaecological surgery. Avoidance of secondhand smoking during the preoperative period may be beneficial for pain management. These findings may have further implications for postoperative pain management after surgery for secondhand smokers.

Conflict of interest The authors received no financial support. The authors have indicated that they have no conflicts of interest regarding the content of this article.

References

1. Pavlin JD, Kent CD. Recovery after ambulatory anesthesia. Curr Opin Anaesthesiol. 2008;21:729–35.
2. Yanagidate F, Dohi S. Epidural oxycodone or morphine following gynaecological surgery. Br J Anaesth. 2004;93:362–7.
3. Tønnesen H. Surgery and smoking at first and second hand: time to act. Anesthesiology. 2011;115:1–3.
4. Creekmore FM, Lugo RA, Weiland KJ. Postoperative opiate analgesia requirements of smokers and nonsmokers. Ann Pharmacother. 2004;38:949–53.
5. Woodside JR Jr. Female smokers have increased postoperative narcotic requirements. J Addict Dis. 2000;19:1–10.
6. Centers for Disease Control and Prevention (CDC). Disparities in secondhand smoke exposure—United States, 1988–1994 and 1999–2004. MMWR Morb Mortal Wkly Rep. 2008;57:744–7.
7. Apfel CC, Roewer N, Korttila K. How to study postoperative nausea and vomiting. Acta Anaesthesiol Scand. 2002;46:921–8.
8. Patrick DL, Cheadle A, Thompson DC, Diehr P, Koepsell T, Kinne S. The validity of self-reported smoking: a review and meta-analysis. Am J Public Health. 1994;84:1086.
9. Seccareccia F, Zuccaro P, Pacifici R, Meli P, Pannozzo F, Freeman KM, Santaquilani A, Giampaoli S; Research Group of the MATISS Project. Serum cotinine as a marker of environmental tobacco smoke exposure in epidemiological studies: the experience of the MATISS project. Eur J Epidemiol. 2003;18(6):487–92.
10. Benowitz NL, Kuyt F, Jacob P III, Jones RT, Osman AL. Cotinine disposition and effects. Clin Pharmacol Ther. 1983;34:604.
11. Lee PN. Misclassification as a factor in passive smoking risk. Lancet. 1986;2:867.
12. Wagenknecht LE, Burke GL, Perkins LL, Haley NJ, Friedman GD. Misclassification of smoking status in the CARDIA study: a comparison of self-report with serum cotinine levels. Am J Public Health. 1992;82:33.
13. Jarvis MJ, Russell MA. Measurement and estimation of smoke dosage to non-smokers from environmental tobacco smoke. Eur J Respir Dis Suppl. 1984;133:68.
14. Hintze J. Power analysis and sample size. NCSS, LLC: Kaysville, Utah; 2008. http//www.ncss.com. Accessed 1st May 2011.
15. Steinmiller CL, Diederichs C, Roehrs TA, Hyde-Nolan M, Roth T, Greenwald MK. Postsurgical patient-controlled opioid self-administration is greater in hospitalized abstinent smokers than nonsmokers. J Opioid Manag. 2012;8(4):227–35.
16. Creekmore FM, Lugo RA, Weiland KJ. Postoperative opiate analgesia requirements of smokers and nonsmokers. Ann Pharmacother. 2004;38:949–53.
17. Woodside JR Jr. Female smokers have increased postoperative narcotic requirements. J Addict Dis. 2000;19:1–10.
18. Stanley TH, DeLang S. The effect of population habits on side effects and narcotic requirements during high dose fentanyl anaesthesia. Can Anaesth Soc J. 1984;31:368–76.
19. Macintyre PE, Jarvis DA. Age is the best predictor of postoperative morphine requirements. Pain. 1996;64:357–64.
20. Morin C, Lund JP, Villarroel T, Clokie CM, Feine JS. Differences between the sexes in post-surgical pain. Pain. 2000;85:79–85.
21. Shi Y, Weingarten TN, Mantilla CB, Hooten WM, Warner DO. Smoking and pain: pathophysiology and clinical implications. Anesthesiology. 2010;113:977–92.
22. Schein JR. Cigarette smoking and clinically significant drug interactions. Ann Pharmacother. 1995;29:1139–48.
23. Sivam SP, Ho IK. Analgesic cross-tolerance between morphine and opioid peptides. Psychopharmacol (Berl). 1984;84:64–5.
24. Pomerleau OF, Fertig JB, Seyler LE, Jaffe J. Neuroendocrine reactivity to nicotine in smokers. Psychopharmacol (Berl). 1983;81:61–7.