Randomized Control Trial

The Effect of Tramadol Versus Sufentanil on Controlling Postoperative Pain for Men Who Smoke and Do Not Smoke: A Randomized Clinical Trial

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Background: Smoking behavior alters the analgesic threshold, which challenges postoperative pain management for patients who smoke.

Objectives: We aimed to assess the analgesic efficacy of tramadol versus sufentanil in relieving postoperative pain for patients who do and do not smoke who underwent a partial hepatectomy.

Study Design: Double-blinded randomized controlled trial.

Setting: Eastern Hepatobiliary Surgery Hospital, Shanghai, China.

Methods: All patients in this study were men. A total of 66 patients who smoke were randomly assigned to receive tramadol or sufentanil (n = 33 each). In addition, a total of 66 patients who do not smoke were randomly assigned to receive tramadol or sufentanil (n = 33 each). The primary outcome was the consumption of additional analgesics within the first 48 hours to control postoperative pain. Secondary outcomes included the postoperative pain level, the frequency of postoperative nausea and vomiting, the sedation score, and the frequency of fever within 48 hours postsurgery.

Results: A significant interaction between "analgesic strategy" and "smoking history" was detected on the consumption of additional analgesics. In those who smoke, the requests for additional doses of analgesics were significantly less in those receiving tramadol than those receiving sufentanil; such a difference was not observed in those who do not smoke. The postoperative pain level was not significantly different between the tramadol group and the sufentanil group within patients who smoke within 48 hours postsurgery. The incidence of treatment-related adverse events was not significantly different between the tramadol group and the sufentanil group within both those who do and do not smoke.

Limitations: Only men patients were included. Also, the superior analgesic effect and the incidence of adverse events of tramadol in patients who smoke were only assessed within the first 48 hours postsurgery.

Conclusions: Our data suggest that tramadol has a better analgesic effect than sufentanil in relieving postoperative pain in patients who smoke.

Key Words: Men patients who smoke, tramadol, sufentanil, postoperative pain management, analgesic efficacy, RCT, analgesic consumption, partial hepatectomy

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Approximately 1.4 billion people smoke cigarettes worldwide (1). Cigarette smoking damages overall health (2) and disrupts pain treatment due, in part, to its regulating changes of the endogenous opioid system (3). In clinical practice, the demand for opioid analgesics (e.g., sufentanil) in patients who smoke is significantly higher, which is accompanied by a series of adverse reactions, such as nausea, vomiting, excessive sedation, respiratory depression, etc (4-6). A refined postoperative pain management strategy is important for the clinical care of patients who smoke.

Nicotine acts as the main addictive component in smoking behavior through binding to nicotinic acetylcholine receptors (nAChRs) (7). Acute nicotine administration results in analgesia (8), yet chronic nicotine exposure leads to changes in the endogenous opioid system (9) and reduces the systemic sensitivity to opioid analgesics (10). Notably, withdrawal from nicotine increases the availability of unbound nAChR ligands (11,12), which suppresses the release of norepinephrine (13) and serotonin (14). These changes result in dysfunction of the descending pain modulation systems (15), which contributes to the poor analgesic effect of opioids for patients who smoke (16-20). During the postoperative period, patients with smoking abstinence, therefore, consume more opioid analgesics for pain relief, which increases the opioid-associated adverse reactions compared to patients who do not smoke (4).

Tramadol is an effective analgesic, which targets the noradrenergic system, serotoninergic system, and opioid system (21). The use of tramadol postoperatively theoretically neutralizes the consequence of nicotine withdrawal for patients who smoke (e.g., the reduced release of norepinephrine [22] and serotonin [23]), thus achieving effective analgesia. However, the different efficacy of analgesics (e.g., tramadol and sufentanil) between patients who do and do not smoke was unclear. Here we aimed to determine whether postoperative use of tramadol could be more effective than other classic opioid analgesics, e.g., sufentanil, for patients who smoke, and to assess the possible difference in treatment effect between patients who do and do not smoke. We therefore performed a double-blinded randomized controlled trial to compare the efficacy of postoperative pain management between tramadol and sufentanil for patients who do and do not smoke.

Methods

Clinical Patients

This study was approved by the Ethical Committee of Medical Research at Eastern Hepatobiliary Surgery Hospital, Shanghai, China (KHBHKY2015-01-007). Written informed consent was obtained from all patients. The trial was registered at the Chinese Clinical Trial Registry (www.chictr.org.cn, ChiCTR-IOR-16008937, principal investigator: Kai Wei, Date of registration: July 2016).

All patients underwent partial hepatectomy due to hepatic occupancy with an American Society of Anesthesiologists Physical Status of I or II. The patients who smoked met the American Psychiatric Association Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) criteria for nicotine dependence, with more than 10 cigarettes per day in the last 6 months and no successful smoking abstinence over one month (24-26). Smoking behaviors, including the average number of cigarettes per day, years of smoking regularly, and duration of smoking abstinence, were recorded. The patients experienced smoking cessation upon admission to the hospital ward. Those who do not smoke reported no history of cigarette use or had smoked $\leq$ 100 cigarettes during their lifetime and had not smoked in the past year.

Patients were excluded for the following: 1) a history of alcohol abuse and drug dependence (other than nicotine for those who smoke), 2) neurological or psychiatric disorders, 3) brain disorders or prior head injury, 4) chronic pain and concomitant analgesic treatments, 5) a body mass index > 28 or < 18, (6) a Child-Pugh score of B or C, 7) serum bilirubin > 42 mmol/L, (8) systolic blood pressure >180 mm Hg or diastolic blood pressure >110 mm Hg, 9) diabetes being treating with insulin, or 10) refusal to use patient-controlled intravenous analgesia (PCIA). Patients who met any of the following criteria during surgery were also excluded: 1) bleeding > 1,000 mL or blood transfusion, 2) surgery time > 3.5 hours or < 1 hour, or 3) severe hemodynamic status instability.

Trial Design and Surgery

The block randomization method was performed to randomize the patients who do and do not smoke into sufentanil (i.e., for smokers: S-S, for nonsmokers: N-S) or tramadol group (i.e., for smokers: S-T, for nonsmokers: N-T), separately. The group assignment was blinded to patients, surgical team, and clinical interviewers. PCIA pumps (containing either sufentanil or

tramadol) were prepared by the planner and delivered to anesthesiologists. All experimental data acquired by the postoperative interviewers were submitted to the planner. The planner would unblind the group assignment if patients had a severe postoperative complication, which was probably relevant to the postoperative analgesics.

The anesthesia program during surgery was identical for all patients. After preoxygenation, induction of anesthesia was achieved with intravenous sufentanil (0.3 μg/kg), cisatracurium (0.2 mg/kg), and target-controlled infusion of propofol (target plasma concentration at 5.0 μg/mL using the Paedfusor model) to facilitate tracheal intubation. Anesthesia was maintained with cisatracurium (1.5 μg/kg/min), remifentanil (0.1-0.2 μg/kg/min), and propofol (target plasma concentration at 3.0-5.0 μg/mL). Mechanical ventilation was adjusted to maintain end-tidal partial pressure of carbon dioxide ($EtCO_2$) between 35 and 45 mm Hg with a tidal volume of 8-10 mL/kg and respiratory rate of 10-14 per minute.

Postoperative pain was controlled using a PCIA strategy (electronic drug infusion pump, ZZB-300, 300 mL, Jiangsu Apon Medical Technology, Co. LTD) to ensure that the pain was lower than or equal to 3 on the Numeric Rating Scale (NRS-11) ranging from 0 (no pain) to 10 (pain as bad as it could be).

Fifteen to 30 minutes prior to the completion of the surgery, all patients started to receive analgesics in the PCIA pump. In the N-S and S-S groups, the PCIA pump contained sufentanil (2 μg/kg) and 20 mg metoclopramide. In the N-T and S-T groups, the PCIA pump contained tramadol (20 mg/kg) and 20 mg metoclopramide. The total capacity of the PCIA pump was 100 mL. The PCIA device was programmed with the following settings: 2 mL/hr basal infusion rate, 2 mL bolus dose, and 15 minute lockout interval. The maximal duration of PCIA was 48 hours.

If patients reported a feeling of moderate pain (NRS-11 > 3) after the surgery, they were allowed to control the pump to release a single dose (2 mL) every 15 minutes in addition to the regular release. When the pain was not relieved after receiving the bolus dose, additional analgesics, including morphine, pethidine, dezocine, fentanyl, parecoxib sodium, or propacetamol, were supplied by our team upon patients' requests (Editor note: Dezocine, parecoxib sodium, and propacetamol are not available for use in the United States.} For all patients, the additional doses of analgesics and postoperative adverse reactions (i.e., nausea and vomiting, sedation, and fever) within 48 hours postsurgery were recorded. Moreover, the subjective ratings of postoperative pain were collected at one, 6, 24, and 48 hours postsurgery.

Outcomes

The primary outcome was the measured consumption of analgesics in addition to the standard doses of analgesics within 48 hours postsurgery (i.e., the analgesics in addition to those in the PCIA pump). To facilitate comparison, the doses of analgesics were first converted to morphine equivalent doses using previously reported conversions (27,28) and then standardized for body weight to obtain the standardized additional morphine equivalent requirement (SAMER, mg/kg). Moreover, the standardized total morphine equivalent requirement, including SAMER and the analgesics in the PCIA pump within 48 hours postsurgery, was also considered in our data analysis.

The secondary outcomes were 1) postoperative pain, 2) the frequency of postoperative nausea and vomiting (PONV), 3) the sedation score using the Ramsay Sedation Scale (29), and 4) the frequency of fever that occurred within 48 hours postsurgery. The safety parameters included respiratory depression, postoperative bleeding, postoperative infection, and wound dehiscence.

Statistical Analysis

To validate the randomization of group assignments, we assessed the balance within patients who do and do not smoke using a standardized difference (30) on a series of patients' baseline characteristics. The detailed demographic information is summarized in Table 1.

To test whether the different analgesic strategies (i.e., sufentanil and tramadol) had different effects on postsurgery SAMER and sedation scores, for both the patients who do and do not smoke, we performed a 2-way analysis of variance (ANOVA) with 2 between-subject factors ("analgesic strategy": sufentanil and tramadol; "smoking history": patients who do and do not smoke). Then, independent-sample t tests were performed to assess the treatment effect of sufentanil versus tramadol within the patients who do and do not smoke, separately. Please note that Shapiro–Wilk tests were conducted to evaluate the normality of the data (i.e., SAMER and the sedation scores). If the values of SAMER and the sedation scores had a skewed distribution (all $P < 0.05$), nonparametric ANOVA, which

constructs null distributions by bootstrap re-sampling (n = 5,000), was performed. Then, Mann-Whitney U tests were performed to assess the treatment effect of sufentanil versus tramadol for the patients who do and do not smoke, separately.

To test whether the different analgesic strategies have different effects on the standardized total morphine equivalent requirement and postoperative pain within 48 hours postsurgery, we performed the a linear mixed effects (LME) model analysis with 2 between-subject factors ("analgesic strategy" and "smoking history") and one within-subject factor ("postoperative time": one, 6, 24, and 48 hours postsurgery) on the standardized total morphine equivalent requirement and postoperative pain.

To assess the treatment effect within the patients who do and do not smoke separately, we performed 2 additional LME model analyses with one between-subject factor (i.e., analgesic strategy) and one within-subject factor (i.e., postoperative time) on the standardized total morphine equivalent requirement and postoperative pain. When there was a significant interaction between the 2 factors, the treatment effect of sufentanil versus tramadol at each postoperative time was compared. To account for multiple comparisons across different postoperative times, a Bonferroni correction was applied to adjust the *P* values. Moreover, Cochran-Mantel-Haenszel tests were performed to assess whether the proportions of patients requiring additional analgesics, the frequency of PONV, and the

Table 1. *Patient baseline characteristics by study groups*[a].

Characteristics	Patients Who Smoke			Patients Who Do Not Smoke		
	Sufentanil Group (n = 33)	Tramadol Group (n = 33)	Standardized Difference	Sufentanil Group (n = 33)	Tramadol Group (n = 33)	Standardized Difference
Age, years	49.5(8.6)	51.0(7.1)	-0.193	52.8(9.5)	51.5(10.2)	0.135
Height, cm	170.8(5.0)	171.7(4.3)	-0.193	169.0(6.5)	169.7(5.8)	-0.123
Weight, kg	69.0(9.6)	67.7(9.0)	0.147	66.0(9.6)	70.2(9.0)	-0.456
BMI, kg/m^2	23.6(2.8)	22.9(2.8)	0.244	23.1(3.2)	24.4(3.2)	-0.399
ABP, mmHg	91.5(6.7)	92.7(11.2)	-0.14	92.8(7.2)	94.1(7.9)	-0.162
HR, bpm	79.0(12.8)	82.8(15.9)	-0.267	78.5(14.0)	75.0(9.3)	0.288
Duration of surgery, min	118.1(41.1)	109.0(45.0)	0.21	112.4(34.1)	107.9(50.4)	0.103
Amount of bleeding, mL	207.6 (162.1)	169.7(122.4)	0.264	180.3(146.3)	190.9(184.8)	-0.064
RBC, $\times 10^{12}/L$	4.6(0.5)	4.6(0.5)	0.065	4.6(0.4)	4.7(0.4)	-0.381
WBC, $\times 10^{12}/L$	6.0(1.8)	5.9(1.5)	0.117	5.1(1.6)	5.1(1.6)	-0.008
Platelet, $\times 10^{9}/L$	190.3(80.6)	177.4(74.8)	0.166	175.5(76.0)	159.8(63.2)	0.225
TB, μmol/L	12.0(4.8)	13.7(4.7)	-0.346	15.1(5.6)	18.1(8.6)	-0.408
DB, μmol/L	4.9(2.3)	4.8(1.8)	0.018	7.4(11.3)	7.1(5.9)	0.034
Albumin, g/L	41.4(3.3)	42.2(3.5)	-0.244	42.6(2.5)	43.5(5.1)	-0.22
Alanine transaminase, U/L	31.6(14.4)	37.5(29.1)	-0.256	31.5(24.9)	45.3(67.2)	-0.272
Glutamic Oxaloacetylase, U/L	27.3(13.1)	32.8(18.6)	0.122	34.9(32.0)	32.9(19.6)	-0.306
Creatinine, μmol/L	74.8(12.8)	77.3(12.1)	-0.2028	85.6(57.4)	85.9(60.3)	-0.005
Glomerular filtration rate, ml/min	106.9(21.3)	102.0(19.4)	0.2428	102.5(18.9)	103.2(19.0)	-0.035
Smoking-related						
Cigarettes per day, numbers	20.0(10.0)	19.5(9.7)	0.0468	0(0)	0(0)	——
Duration of smoking, years	22.4(7.1)	25.6(7.8)	-0.428	0(0)	0(0)	——
Duration of abstinence, days	8.7(6.9)	8.5(6.7)	0.018	0(0)	0(0)	——
Cotinine in plasma, ng/ml	22.6(35.6)	25.6(38.5)	-0.081	0(0)	1.6(9.1)	-0.254
Cotinine in urine, ng/ml	143.7(223.0)	176.3(273.4)	-0.133	12.7(61.5)	13.2(59.2)	-0.007

Abbreviations: BMI, body mass index; ABP, average blood pressure; HR, heart rate; RBC, red blood cell; WBC, white blood cell; TB, total bilirubin; DB, direct bilirubin. [a] Data are reported as mean (standard deviation) unless otherwise indicated. Standardized difference = difference in means or proportions divided by standard error; imbalance defined as an absolute value greater than 0.4825 (small effect size).

frequency of fever were different between the tramadol group and the sufentanil group within the patients who do and do not smoke separately. The treatment effect of sufentanil versus tramadol on these variables was also assessed using relative risk (CI) for the patients who do and do not smoke separately.

All statistical analyses were carried out in SPSS 17.0 (SPSS Inc.) and the statistical significance level was set at 0.05.

Sample Size Calculation

A preliminary study was performed on 30 patients who smoke and 30 who do not smoke. The experiment procedure was identical to the formal experiment in the present study. Based on the results of the preliminary study, a sample size of 120 patients (30 patients in the sufentanil group and 30 patients in the tramadol group for both patients who do and do not smoke) was required to provide a power of $(1-\beta) = 0.90$, assuming a 2-sided significant level at $\alpha = 0.05$, the mean values of SAMER in each group obtained from the preliminary study (N-S: 0.08 mg/kg, N-T: 0.14 mg/kg, S-S: 0.20 mg/kg, and S-T:0.03 mg/kg), and their pooled standard deviation = 0.1821 using one-way ANOVA in Power Analysis & Sample Size 15.0.3 (NCSS Statistical Software). To compensate for a follow-up attrition rate of 10%, the sample size was increased to 132 patients.

Results

A total of 297 men receiving a partial hepatectomy were recruited in the Eastern Hepatobiliary Surgery Hospital, Shanghai, China, from July 2016 through March 2017. Of these patients, 132 patients completed the study, in which 66 patients who smoke were randomly assigned to receive tramadol or sufentanil, and 66 patients who do not smoke were randomly assigned to receive tramadol or sufentanil (Fig. 1). All baseline characteristics of the patients were well balanced for those who do and do not smoke (Table 1).

Primary Outcome

For the primary outcome, results showed that the values of SAMER had a skewed distribution (all $P < 0.05$). Then, nonparametric ANOVA was performed and showed a significant main effect of "analgesic strategy" ($P = 0.001$, 95% CI, 0.081 to 0.276) and a significant interaction between the 2 factors ($P = 0.001$, 95% CI, -0.348 to -0.087, Fig. 2A). No significant main effect of "smoking history" ($P = 0.474$, 95% CI, -0.054 to 0.114) was detected.

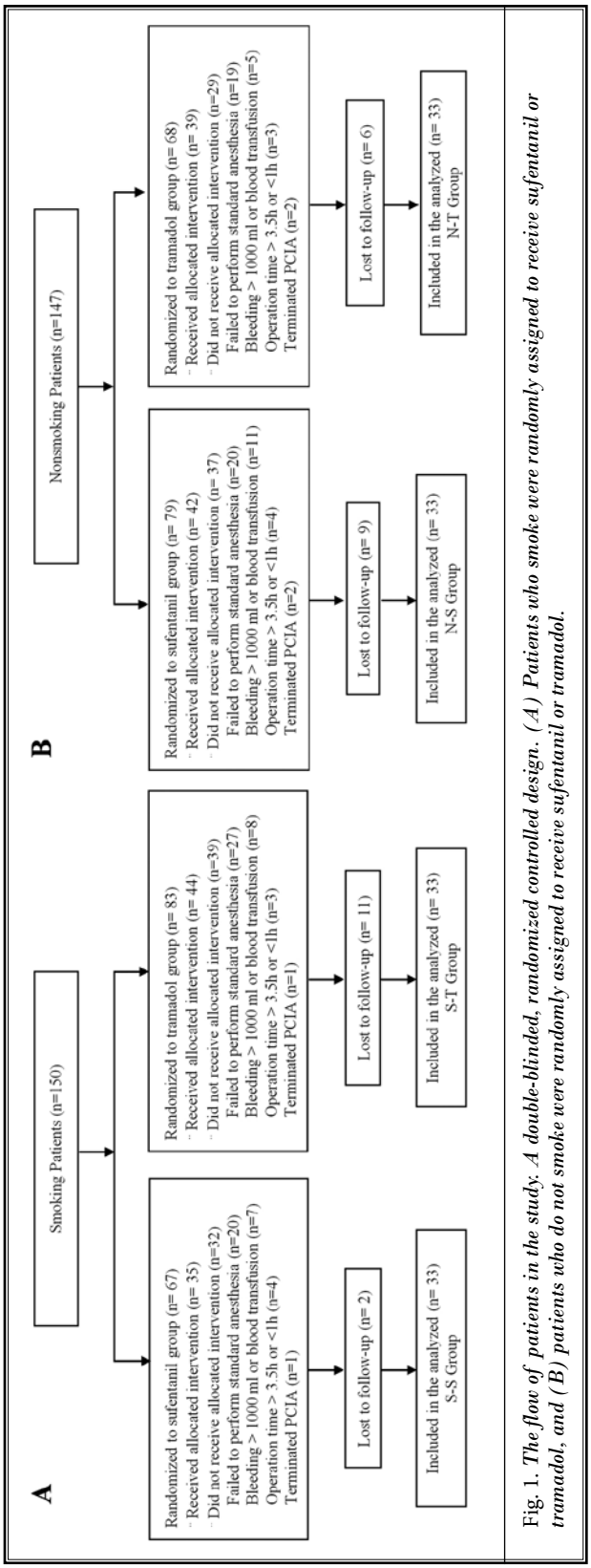

Fig. 1. *The flow of patients in the study. A double-blinded, randomized controlled design. (A) Patients who smoke were randomly assigned to receive sufentanil or tramadol, and (B) patients who do not smoke were randomly assigned to receive sufentanil or tramadol.*

Mann-Whitney U-tests showed that the SAMER was significantly larger for the sufentanil group than the tramadol group for patients who smoke ($P < 0.001$). For patients who do not smoke, the SAMER was not significantly different between the tramadol group and the sufentanil group ($P = 0.361$, Fig. 2A).

Results from the Breslow-Day test showed that there was a heterogeneity of treatment effect on the numbers of requiring additional analgesics between patients who do and do not smoke ($\chi^2 = 15.709$, degrees of freedom [df] = 1, $P < 0.001$). Cochran-Mantel-Haenszel tests showed that the proportion of patients requiring additional analgesics was significantly larger for the sufentanil group than the tramadol group for patients who smoke (90.9% vs. 45.5%, $P < 0.001$; Fig. 2B and Table 2). In contrast, for patients who do not smoke, the proportion requiring additional analgesics was not significantly different between the tramadol group and the sufentanil group (51.5% vs. 69.7%, $P = 0.131$; Fig. 2B and Table 2).

The total morphine equivalents, including SAMER and the analgesics in the PCIA pump within 48 hours postsurgery, were 139.26 ± 20.62 mg for N-S, 150.86 ± 21.35 mg for N-T, 158.25 ± 25.19 mg for S-S, and 143.15 ± 20.22 mg for S-T. For the standardized total morphine equivalent requirement within 48 hours postsurgery, LME model analysis showed significant main effects of "postoperative time," "analgesic strategy," and "smoking history," and a significant interaction among the 3 factors (Table 3).

To examine the treatment effects for patients who smoke and do not smoke, a significant main effect of "postoperative time" was observed for patients who do not smoke. No significant main effect of "analgesic strategy" and interaction between the 2 factors was found for patients who do not smoke. Moreover, significant main effects of "postoperative time" and "analgesic strategy" as well as a significant interaction between the 2 factors were observed for patients who smoke. The standardized total morphine equivalent requirement was not significantly different between the tramadol group and the sufentanil group for patients who do not smoke within 48 hours postsurgery. However, the standardized total morphine equivalent requirement was significantly higher for the sufentanil group than the tramadol group for patients who smoke at 6 hours ($P = 0.038$, 95% CI, 0.006 – 0.201), 24 hours ($P < 0.001$, 95% CI, 0.172 – 0.367), and 48 hours ($P < 0.001$, 95% CI, 0.082 – 0.277) postsurgery (Fig. 3A).

Secondary Outcomes

For postoperative pain within 48 hours postsurgery, LME model analysis showed significant main ef-

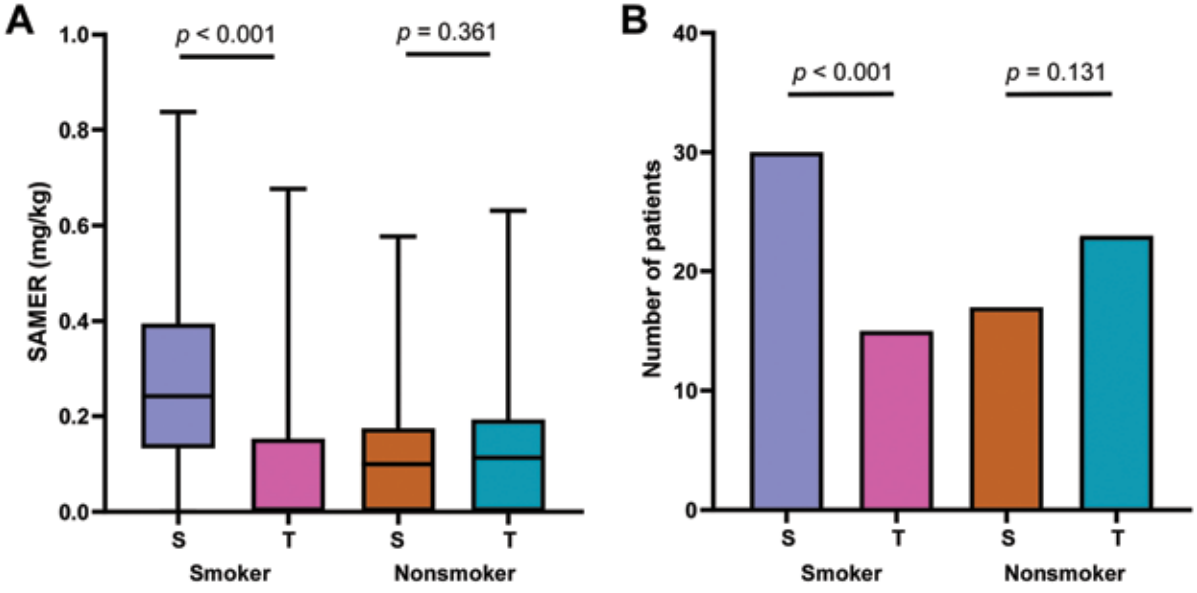

Fig. 2. *The treatment effect of sufentanil versus tramadol on the primary outcome for patients who do and do not smoke. A: the standardized additional morphine equivalent requirement (SAMER); B: the numbers of patients using additional analgesics. S, sufentanil; T, tramadol.*

fects of "postoperative time" and "analgesic strategy." No significant main effect of "smoking history" or interaction between these factors was detected (Table 3). To examine the treatment effects within patients who do and do not smoke, a significant main effect of "postoperative time" was observed within the patients who smoke. Moreover, significant main effects of "postoperative time" and "analgesic strategy" were observed within patients who do not smoke. There was no significant interaction between the 2 factors within both patients who do and do not smoke (Table 3). The postoperative pain level was not significantly different between the tramadol group and the sufentanil group within patients who smoke within 48 hours postsurgery. However, postoperative pain was significantly higher for the sufentanil group than the tramadol group within patients who do not smoke at 6 hours (P = 0.037) and 48 hours (P < 0.001) postsurgery (Fig. 3B and Table 2).

Moreover, Breslow-Day tests showed that there was no heterogeneity of treatment effect between patients who do and do not smoke on the frequency of PONV (χ^2 = 0.703, df = 1, P = 0.402) and the frequency of fever (χ^2 =0.645, df = 1, P = 0.422) occurred within the 48

Table 2. *Primary and secondary outcomesa*.

Variables	Treatment Effect for Patients Who Smoke					
	Sufentanil Group (n=33)	Tramadol Group (n=33)	$\chi^2(1)$	*P* Value	Odds Ratio	95% CI
Primary Outcome						
SAMER, mg/kg[f]	0.30(0.23)	0.12(0.19)	-	< 0.001	-	-
Patients requiring additional analgesics, numbers[e]	30	15	15.714	< 0.001	12	3.048-47.244
Secondary Outcomes						
Postoperative pain ratings[b,d]						
One hour	5.0(1.1)	5.1 (1.3)	-	0.835	-	-0.631 to 0.510
6 hours	3.7(1.2)	3.6(1.5)	-	0.754	-	-0.479 to 0.661
24 hours	2.2(1.3)	1.7(1.1)	-	0.061	-	-0.025 to 1.116
48 hours	1.0(1.2)	0.6(0.9)	-	0.211	-	-0.207 to 0.934
PONV, numbers[e]	5	4	0.129	0.72	1.295	0.315-5.322
Fever, numberse	5	5	0	1	1	0.260-3.841
The sedation score[c,f]	2.0(0.1)	2.0(0.1)	-	0.558	-	-
Variables	**Treatment Effect for Patients Who Do Not Smoke**					
	Sufentanil Group (n=33)	Tramadol Group (n=33)	$\chi^2(1)$	*P* value	Odds Ratio	95% CI
Primary Outcome						
SAMER, mg/kg[f]	0.11(0.15)	0.15(0.16)	-	0.361	-	-
Patients requiring additional analgesics, numbers[e]	17	23	2.285	0.131	0.462	0.168-1.267
Secondary Outcomes						
Postoperative pain ratings[b,d]						
1 hour	4.8 (1.3)	4.5(1.0)	-	0.348	-	-0.298 to 0.843
6 hours	3.5(1.5)	2.9(1.0)	-	0.037	-	0.036-1.176
24 hours	2.2(1.2)	1.6(1.0)	-	0.061	-	-0.025 to 1.116
48 hours	1.4(1.5)	0.5(0.7)	-	<0.001	-	0.521-1.661
PONV, numbers[e]	6	9	0.776	0.378	0.593	0.184-1.910
Fever, numbers[e]	9	5	1.451	0.228	2.1	0.619-7.125
The sedation score[c,f]	2.0(0.1)	2.0(0.1)	-	0.649	-	-

Abbreviations: SAMER, standardized additional morphine equivalent requirement; PONV, postoperative nausea and vomiting. [a] Data are reported as mean (standard deviation) unless otherwise indicated. [b] Postoperative pain was rated on a Numeric Rating Scale (NRS-11)ranging from 0 (no pain) to 10 (pain as bad as it could be). [c] The sedation score was evaluated using the Ramsay Sedation Scale. [d] LME model analysis. [e] Cochran-Mantel-Haenszel test. [f] Mann-Whitney U-tests.

hours after the surgery. Cochran-Mantel-Haenszel tests showed that the frequency of PONV and the frequency of fever that occurred within 48 hours postsurgery were not significantly different between the tramadol group and the sufentanil group within patients who do and do not smoke (all $P > 0.05$, Table 2).

For the sedation score within 48 hours postsurgery, results showed that the values of the sedation score had a skewed distribution (all $P < 0.05$). Therefore, nonparametric ANOVA was performed and showed no significant main effects of "analgesic strategy" ($P = 0.329$, 95% CI, -0.076 to 0.017) and "smoking history" ($P = 0.961$, 95% CI, -0.041 to 0.034), as well as their interaction ($P = 0.849$, 95% CI, -0.054 to 0.069; Fig. 2A and Table 2). Mann-Whitney U tests showed that the sedation score was not significantly different between the tramadol group and the sufentanil group within patients who smoke ($P = 0.558$) and patients who do not smoke ($P = 0.649$; Table 2). There were no severe complications, such as respiratory depression, hypotension, postoperative bleeding, postoperative infection, and wound dehiscence within 48 hours postsurgery for all patients.

Table 3. *LME model analysis to assess the effects of "analgesic strategy," "smoking history," and "postoperative time" on standardized total morphine equivalent requirement and the perceived intensity of postoperative pain.*

Standardized Total Morphine Equivalent Requirement	**df**	**F value**	***P* Value[a]**
Patients Who Do and Do Not Smoke			
Analgesic strategy	(1, 120.712)	5.431	0.021
Smoking history	(1, 120.712)	9.561	0.002
Postoperative time	(3, 198.157)	5411.824	< 0.001
Analgesic strategy × Smoking history	(1, 120.712)	9.802	0.002
Analgesic strategy × Postoperative time	(3, 198.157)	5.265	0.002
Smoking history × Postoperative time	(3, 198.157)	5.204	0.002
Analgesic strategy × Smoking history × Postoperative time	(3, 198.157)	7.167	< 0.001
Patients Who Do Not Smoke			
Analgesic strategy	(1,62.384)	0.415	0.522
Postoperative time	(3,116.250)	3622.311	< 0.001
Analgesic strategy × Postoperative time	(3,116.250)	0.309	0.819
Patients Who Smoke			
Analgesic strategy	(1,56.568)	12.307	0.001
Postoperative time	(3,77.691)	2071.643	< 0.001
Analgesic strategy × Postoperative time	(3,77.691)	10.222	< 0.001
Perceived Intensity of Postoperative Pain	**df**	**F value**	***P* value[a]**
Patients Who Do and Do Not Smoke			
Analgesic strategy	(1,135.394)	7.568	0.007
Smoking history	(1,135.394)	1.698	0.195
Postoperative time	(3,236.662)	338.895	< 0.001
Analgesic strategy × Smoking history	(1,135.394)	1.575	0.212
Analgesic strategy × Postoperative time	(3,236.662)	2.005	0.114
Smoking history × Postoperative time	(3,236.662)	1.239	0.296
Analgesic strategy × Smoking history × Postoperative time	(3,236.662)	1.651	0.178
Patients Who Do Not Smoke			
Analgesic strategy	(1,65.958)	8.617	0.005
Postoperative time	(3,123.234)	160.523	<0.001
Analgesic strategy × Postoperative time	(3,123.234)	2.265	0.084
Patients Who Smoke			
Analgesic strategy	(1,75.347)	1.043	0.31
Postoperative time	(3,187.584)	187.554	< 0.001
Analgesic strategy × Postoperative time	(3,187.584)	1.408	0.242

[a] *P* value of less than 0.05 was considered significant.

Discussion

Accumulating evidence suggests that patients who smoke who are deprived of cigarettes experience greater pain sensitivity (31-33) and require a higher quantity of postoperative opioid analgesics than patients who do not smoke (4). This indicates that the use of opioid analgesics to manage postoperative pain for patients who smoke who are abstaining might not be an optimal solution. Currently, how to effectively manage postoperative pain for patients who smoke remains a priority for anesthesiology research.

Given the possible neural mechanism of hyperalgesia in patients who smoke who

are abstaining, and the analgesic effect of serotonin (34), Qiu and colleagues (34) proposed that the use of tramadol to cope with postoperative pain for patients who smoke who are abstaining might be an effective treatment strategy. To test this hypothesis, for the first time, we compared the treatment effect of sufentanil (an opioid analgesic) versus tramadol (a serotonin analgesic) in postoperative pain management in both patients who smoke who are abstaining and patients who do not smoke using a double-blind randomized controlled design. Our results indicate that tramadol showed a better analgesic effect than sufentanil on postoperative pain relief in patients who smoke who are abstaining, without inducing more adverse effects. However, no difference in treatment effect between sufentanil and tramadol was observed in patients who do not smoke. These results may suggest that tramadol could be considered for postoperative pain management for patients who smoke, although a large sample size study is needed to verify our findings.

Consistent with previous clinical studies (4), we observed that patients who smoke who are abstaining demanded higher doses of opioids during the first 48 hours postsurgery than patients who do not smoke,

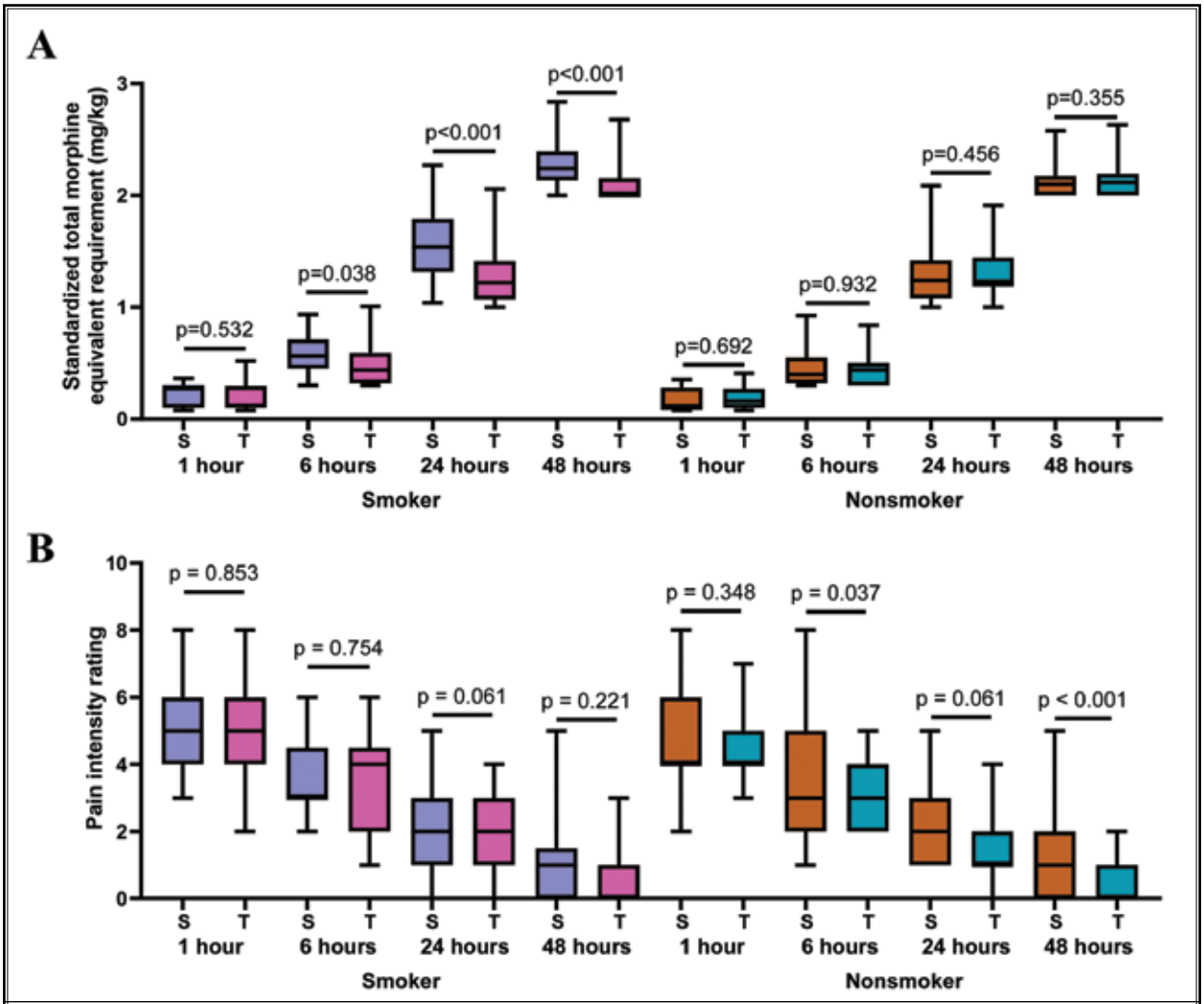

Fig. 3. *The treatment effect of sufentanil versus tramadol on (A) the standardized total morphine equivalent requirement and (B) postoperative pain level for patients who do and do not smoke. The standardized total morphine equivalent requirement and subjective ratings of postoperative pain are presented at one hour, 6 hours, 24 hours, and 48 hours postsurgery. S, sufentanil; T, tramadol.*

which demonstrates the dysfunction of the endogenous opioid system in patients who smoke who are abstaining. Therefore, using opioid analgesics to relieve postoperative pain for patients who smoke who are abstaining might not be an optimal strategy.

The serotonergic system plays an important role in modulating pain processing (35). According to the possible mechanisms of nicotine withdrawal, increasing the concentration of serotonin in vesicles in neurons of the brain and spinal cord might be an effective treatment to relieve postoperative pain for patients who smoke who are abstaining (34). Tramadol increases extracellular concentrations of norepinephrine and serotonin (36,37), therefore it might act beyond the endogenous opioid system and is superior to opioid analgesics under this circumstance. In line with this hypothesis, we here report that the use of tramadol decreased the demand for analgesics for patients who smoke: nearly 60% less SAMER was required for patients who smoke with tramadol than those given sufentanil. Meanwhile, fewer patients who smoke given tramadol required additional analgesics than those given sufentanil. Even fewer analgesics were required for patients who smoke given tramadol; the analgesic effect was stronger than those given sufentanil at 24 and 48 hours postsurgery, i.e., postoperative pain was lower for tramadol groups than for sufentanil groups (Fig. 2 and Table 2).

Nicotine has antinociceptive effects. To cope with postoperative pain, nicotine has been investigated as an adjunctive medication for postoperative pain management in patients who smoke who are abstaining (38). However, nicotine alone is likely not enough to control postoperative pain (38). Therefore, finding other effective treatment strategies to cope with postoperative pain for patients who smoke who are abstaining should be prioritized for anesthesiology research. In the current study, we demonstrate the superior analgesic effect of tramadol over sufentanil on postoperative pain relief in patients who smoke who are abstaining without inducing more adverse effects. Meanwhile, no differences in treatment effects were detected in patients who do not smoke.

These findings suggested that tramadol might be an effective analgesic to manage perioperative pain for patients who smoke who are abstaining. Future trials are required to assess the safety profile and clinical analgesic effect of tramadol in perioperative pain management in patients who smoke who undergo other types of surgeries. Besides, nicotine replacement therapy aims to reduce withdrawal symptoms associated with stopping smoking by replacing the nicotine from cigarettes. Considering that nicotine replenishment could neutralize the consequence of the sudden increase of unbound nAChR ligands caused by nicotine withdrawal, and that tramadol could be an effective analgesic to manage perioperative pain for patients who smoke who are abstaining, nicotine replacement therapy plus tramadol should be considered in future studies to refine postoperative pain management for patients who smoke who are abstaining.

Limitations

This study has some limitations. First, only men were included in the present study. It will be important to understand if the conclusion could be generalized to women or to other types of surgeries. Second, the superior analgesic effect and the incidence of adverse events of tramadol in patients who smoke were only assessed within the first 48 hours postsurgery. The long-term (more than 48 hours) effects should be assessed in future studies. Third, it will be important to understand if norepinephrine and serotonin systems act equivalently in postoperative pain control by tramadol. Dissecting the pharmacological mechanisms would further improve the pain management strategy for patients who smoke.

Conclusions

Our data suggest that tramadol is more effective in relieving postoperative pain than sufentanil for patients who smoke who had a partial hepatectomy but warrants further study with a larger sample size.

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