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ORIGINAL RESEARCH

Effect of Preadministration of Nalmefene on Sufentanil-Induced Cough During Induction of General Anesthesia in Patients Undergoing Breast Surgery: A Double-Blind Randomized Controlled Trial

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Purpose: This study was designed to investigate the effects of preadministration of nalmefene before general anesthesia induction on sufentanil-induced cough (SIC) in patients undergoing breast surgery.

Patients and Methods: A total of 105 patients scheduled for elective breast surgery under general anesthesia were selected and randomly assigned into three groups: normal saline (Group C), low-dose nalmefene 0.1 $\mu g \cdot kg^{-1}$ (Group LN), and high-dose nalmefene 0.25 $\mu g \cdot kg^{-1}$ (Group HN). Sufentanil 0.5 $\mu g \cdot kg^{-1}$ was injected intravenously within 2 s after 5 min of intervention. The count and severity of cough within 2 min after sufentanil injection, as well as the time to first cough, were recorded. In addition, we also collected intraoperative hemodynamic data, postoperative pain scores, the incidence of receiving rescue analgesics, and side effects up to 24 h after surgery.

Results: Compared to Group C, the incidence of SIC was significantly lower in Group LN and HN (64.7% vs 30.3% and 14.7%, respectively; $P < 0.001$), but no significant difference was observed between the two groups (P=0.126). Compared to Group C, the risk factors decreased by 53.4% (95% confidence interval [CI] =0.181–0.735, P=0.008) in Group LN and by 75.9% (95% CI=0.432–0.898, P=0.001) in Group HN. Of the patients with SIC, less frequent SIC within 2 min after induction and a lower proportion of severe coughs were observed than Group C ($P < 0.05$), and no difference was detected between Group LN and HN. Additionally, the onset time to the first SIC did not differ significantly between the groups. Intraoperative hemodynamic data, postoperative pain scores, and side effects in the first 24 h did not differ among the groups.

Conclusion: Preadministration of nalmefene prior to induction of general anesthesia effectively suppressed SIC in patients undergoing breast surgery, without affecting intraoperative hemodynamic fluctuation and postoperative pain intensity.

Keywords: nalmefene, general anesthesia, sufentanil, cough, breast surgery

Introduction

Sufentanil, a potent mu-opioid receptor agonist with rapid action, strong analgesic, prolonged duration, stable hemodynamics, and a high treatment index, is an ideal opioid analgesic in the induction of general anesthesia.[1,2] However, sufentanil-induced cough (SIC) is common in anesthesia practice.[3,4] Sometimes, the cough is mild and self-limiting, but

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when it is severe, SIC can increase the risk of aspiration pneumonia,[5] postoperative nausea and vomiting,[6] and even undesirable pressure increase in the coelomic cavity, which can lead to severe adverse outcomes in critically ill patients. A severe cough reflex may also cause multiple subconjunctival hemorrhages and periorbital ecchymosis,[7] and further increase the risk of aspiration pneumonia.[8] Therefore, SIC prevention is urgently required.

Although the precise mechanism underlying SIC remains unclear, it is widely believed that the agonistic effect of mu2-opioid receptors located on the surface of the tracheobronchial tree plays a significant role.[9,10] In clinical settings, nalmefene, a mu-/delta-opioid receptor antagonist and kappa-opioid receptor partial agonist,[11] is used to reverse opioid side effects.[12,13] The side effects associated with nalmefene are mild, including nausea or vomiting. Animal experiments have shown the cough-depressant effects of opioid antagonists on the capsaicin-induced cough reflex in mice and rats.[14–16] However, it has not yet been determined whether the antitussive effect of opioid antagonists affects SIC in surgical patients.

This randomized trial aimed to test the hypothesis that the preadministration of nalmefene before induction of general anesthesia inhibits SIC in patients undergoing breast surgery.

Materials and Methods

Study Design

This prospective, double-blind, single-center, parallel-group, randomized controlled trial was approved (SL-B2021-337-02) by the Ethics Committee of the Sun Yat-sen University Cancer Center (Guangzhou, China) and registered with the Chinese Clinical Trial Registry (ChiCTR2200055139, Date of registration: January 1, 2022) prior to patient enrollment. All participants provided written informed consent. This study adhered to the guidelines of the Consolidated Standards of Reporting Trials (CONSORT) and complied with the Declaration of Helsinki.

Trial Participants

This study enrolled patients who underwent breast surgery under general anesthesia at Sun Yat-sen University Cancer Center between March 2022 and January 2023. Patients, aged 18–65 years, of both sexes, who were classified as American Society of Anesthesiologists (ASA) physical status I or II, were eligible for the trial. The exclusion criteria were as follows: long-term treatment with angiotensin-converting enzyme inhibitors (ACEI), angiotensin II receptor blockers (ARB), bronchodilators, or glucocorticoids; a history of allergy to anesthetics; predicted difficult airway; high intracranial, intra-abdominal, or intraocular pressure; psychiatric disorders, neurological disease, renal or hepatic insufficiency; uncontrolled hypertension; respiratory diseases, such as asthma, upper respiratory tract infection (URTI); and chronic obstructive pulmonary disease (COPD).

Randomization and Blinding

After obtaining informed consent, eligible patients were randomly assigned to one of the three groups using a code sealed in envelope. The code was obtained from a computer-generated random sequence. The patients, anesthetists involved in perioperative management, and the investigator who responded for preoperative assessment, postoperative follow-up, and data collection, were blinded to the allocation sequence. On the morning of surgery, each syringe (containing either nalmefene or saline) was prepared by a research nurse blinded to the study protocol, according to the patient's code in the envelope. To ensure that the syringes were visually identical, all the drugs were diluted in 0.9% saline to a total volume of 10 mL.

Anesthesia Protocol

After entering the operating room, all patients were monitored using electrocardiography (ECG). Peripheral capillary oxygen saturation (SPO_2), non-invasive blood pressure (NIBP), heart rate (HR), axillary temperature, and Narcotrend index were monitored, and intravenous access was established. Prior to anesthesia induction, an equivalent dose of saline was administered to patients in Group C, 0.1 $\mu g \cdot kg^{-1}$ of nalmefene was administrated to the patients in Group LN, and 0.25 $\mu g \cdot kg^{-1}$ of nalmefene was administrated to the patients in Group HN. Five minutes later, 0.04 $mg \cdot kg^{-1}$ of midazolam was administered till the patient fell asleep, and then, sufentanil 0.5 $\mu g \cdot kg^{-1}$ was injected intravenously within 2 s. Anesthesia induction was achieved using 1.5 $mg \cdot kg^{-1}$ of propofol and 0.2 $mg \cdot kg^{-1}$ of cis-atracurium.

Endotracheal intubation was performed with a visual laryngoscope following facemask-assisted ventilation and complete muscle relaxation. General anesthesia was maintained with intravenous remifentanil at 0.02–0.2 μg·kg^{-1}·minute^{-1} and cis-atracurium at 2 μg·kg^{-1}·minute^{-1}. Sevoflurane was supplied initially at 1.3 minimal alveolar concentration (MAC) to achieve a Narcotrend index of 40–60. Under volume-controlled ventilation, adjustments were made to ensure 0.5 fraction of oxygen (FiO_2), 6–8 mL·kg^{-1}of tidal volume, and a respiratory rate of 12–15 per min, for normocapnia (end-tidal carbon dioxide 35–45 mm Hg). Bradycardia (HR < 45 beats min^{-1}) or persistent hypotension (mean arterial pressure [MAP] <60 mm Hg) were treated with additional fluid infusion, atropine (0.3 mg), or dopamine (2 mg) at the time of incision suture. Palonosetron (0.25 mg) was administrated to prevent postoperative nausea and vomiting (PONV) and 50 mg of flurbiprofen was added for postoperative analgesia. At the end of surgery, remifentanil and sevoflurane were discontinued. Tracheal extubation was performed when the Narcotrend index exceeded 80, the patients responded to verbal commands, and they had adequate spontaneous breathing (respiratory rate >12/min and SPO_2 > 95% for at least 5 min when breathing air). Patients were sent to the ward when their Aldrete scores reached 9 or 10.

Outcome Measures

All data were prospectively collected by a researcher who was blinded to the group assignments. Baseline data on patients, surgery, and anesthesia were obtained. Total doses of remifentanil, dopamine, and atropine were documented. The MAP and HR were measured at baseline, after anesthesia induction, after endotracheal intubation, 3 min after skin incision, and at extubation. The incidence of SIC was evaluated within 2 min of sufentanil administration. The counts of cough and the onset time to first cough were recorded. The severity of SIC was then determined based on the count of coughs (mild, 1–2; moderate, 3–4; and severe, >4).[17]

All patients were followed up for 24 h after surgery by the same blinded investigator. Postoperative pain intensity was assessed at rest using an 11-point numerical rating scale (NRS) (score range, 0 [no pain] to 10 [worst pain imaginable]) at 4–6 h and 24 h postoperatively. If patients required analgesics or an NRS score >4 was detected, 50 mg of flurbiprofen was administered, and the number of rescue analgesic medications was documented. The following opioid-related adverse effects were monitored: nausea, vomiting, drowsiness, dizziness, headache, shivering, fever, hypotension, urinary retention, and pruritus.

The primary outcome was the incidence of SIC following sufentanil administration. Secondary outcomes included SIC severity, onset time to the first cough, MAP, and HR at five set time points, postoperative pain intensity at postoperative 4–6 h and 24 h; incidence of rescue analgesic demand, and postoperative opioid-related side effects.

Sample Size Calculation

In our pilot study (n=10), the incidence of SIC following injection of sufentanil (0.5 μg·kg^{-1}) through a peripheral intravenous line within 2 s was 70%. We hypothesized that nalmefene would reduce the incidence of SIC by 50%. With a risk of type-I error of 0.05, a power of 0.8, and a 20% dropout rate, 35 participants were required in each group.

Statistical Analysis

All statistical analyses were performed using SPSS version 25 (IBM Corp., Armonk, NY, USA). The Shapiro–Wilk test was used to determine the normality of the data distribution. Levene's test was used to verify the homogeneity of the variance. Post hoc comparisons were conducted using Bonferroni adjustment. Categorical variables were presented as frequencies (proportions). Continuous variables were presented as mean ± standard deviation (SD) if they were normally distributed and median (interquartile range [IQR]) if they were not. Data on patient characteristics, surgery, and anesthesia were analyzed using a one-way analysis of variance (ANOVA) for continuous variables if normally distributed. Kruskal–Wallis test was performed if the data is not normally distributed, and the Pearson $\chi 2$ or Fisher exact tests for categorical variables. The incidence of SIC was compared by Pearson $\chi 2$ or Fisher exact tests, and relative risks (RR) with 95% confidence interval (CI) were calculated using the robust Poisson regression model to adjust the bias of different ages and intravenous access. The severity of SIC, the incidence of postoperative opioid-related adverse effects, and the requirement for rescue analgesics were also evaluated using the Pearson $\chi 2$ or Fisher exact tests. One-way ANOVA was used to compare the onset times of the first cough. The NRS scores at postoperative 4–6 h and 24 h were

evaluated using a generalized linear model to remove the potential influence of age, surgical approaches, and surgeons. The hemodynamic data at each time point were analyzed using repeated-measures ANOVA. Imputation techniques were not applied to the missing data. Bonferroni-adjusted P values are presented for pairwise comparisons. Statistical significance was set at $P < 0.05$. significant.

Results

Characteristics of the Patients, Surgery, and Anesthesia

Among the 113 patients assessed for eligibility, 105 consented to participate and were randomly assigned to one of the three groups, with 35 participants per group. Four patients were lost to follow-up. Finally, 34 patients were allocated to Group C, 33 to Group LN, and 34 to Group HN, totaling 101 patients (Figure 1). The overall baseline and clinical patient characteristics (Table 1) and intraoperative anesthesia data (Table 2) were similar among the three groups.

Sufentanil-Induced Cough

A visualization of SIC occurrence in each group is shown in Figure 2. SIC was less prevalent in Group LN (Table 3; 64.7% vs 30.3%, $P = 0.005$) and Group HN (Table 3; 64.7% vs 14.7%, $P < 0.001$) than in Group C during the observation window following sufentanil administration. However, no significant differences were observed between Group LN and HN (Table 3; 30.3% vs 14.7%, $P = 0.126$). The risk of developing SIC was significantly reduced in Group LN (Table 3; RR = 0.466, 95% CI = 0.265–0.819, $P = 0.008$) and Group HN (Table 3; RR = 0.241, 95% CI = 0.102–0.568, $P = 0.001$) compared with patients who received a placebo (Group C). However, no significant difference was observed between Group LN and HN (RR = 0.516, 95% CI = 0.196–0.641, $P = 0.181$). Of the patients with SIC, fewer coughs were observed in Group LN (Table 3; 2[0–4] vs 0[0–2], $P = 0.006$) than Group HN (Table 3; 2[0–4] vs 0[0–0], $P < 0.001$), indicating a significant difference in SIC severity ($P = 0.001$), which is characterized by a higher proportion of severe cough in Group C (Table 3; 20.6% vs 12.1% vs 8.8%). In addition, there was no difference in the time to onset of the first cough between the two experimental groups.

Hemodynamic Data

Hemodynamic data are shown in Figure 3 (MAP [A] and HR [B]). Intergroup comparisons of MAP and HR at the five predetermined time points did not differ significantly. However, the MAP and HR in all groups at all time points other than baseline were significantly different from their respective baseline values ($P < 0.001$). Additionally, repeated measures ANOVA revealed that MAP ($P = 0.218$) and HR ($P = 0.339$) changed in a statistically significant manner

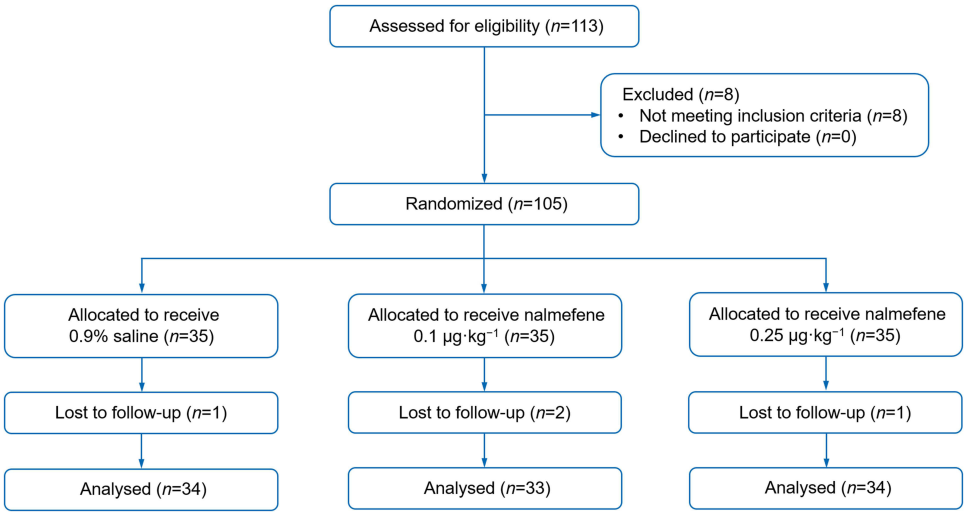

Figure 1 CONSORT diagram of patient recruitment.

Table 1 Characteristics of Patients and Surgery

	Group C (n=34)	Group LN (n=33)	Group HN (n=34)	*P*
Age (y)	48.2±8.4	45.7±8.4	47.2±9.3	0.511
Sex (male/female)	0/34	0/33	0/34	–
BMI ($kg \cdot m^{-2}$)	23.0±3.3	22.9±2.8	22.0±3.5	0.354
ASA (I/II)	19/15	17/16	19/15	0.918
Hypertension	3 (8.8%)	2 (6.1%)	2 (5.9%)	0.867
Diabetes	0	1 (3.0%)	0	0.353
Smoking	0	0	0	–
Intravenous access (Peripheral/Central)	29/5	27/6	32/2	0.299
Surgery				0.936
Modified radical mastectomy	22 (64.7%)	18 (54.5%)	19 (55.9%)	
Simple mastectomy	7 (20.6%)	7 (21.2%)	6 (17.6%)	
Lumpectomy	3 (8.8%)	4 (12.1%)	5 (14.7%)	
Nipple-sparing mastectomy	2 (5.9%)	4 (12.1%)	4 (11.8%)	

Note: Values are mean ± SD or number (proportion).
Abbreviations: BMI, Body Mass Index; ASA, American Society of Anesthesiologists; LN, low-dose nalmefene 0.1 $\mu g \cdot kg^{-1}$; HN, high-dose nalmefene 0.25 $\mu g \cdot kg^{-1}$; C, control, normal saline; SD, standard deviation.

Table 2 Characteristics of Anesthesia and Postoperative Pain Intensity

	Group C (n=34)	Group LN (n=33)	Group HN (n=34)	*P*
Duration of anesthesia (min)	104.4±27.1	94.7±31.5	114.4±44.8	0.078
Extubation time (min)	19.4±7.6	18.8±5.0	18.2±5.4	0.720
Recovery time (min)	25 (20–36.25)	30 (25–35)	30 (23.75–30)	0.865
Amount of remifentanil (μg)	0.24±0.10	0.22±0.12	0.26±0.13	0.414
Patients receiving dopamine	14 (41.2%)	10 (30.3%)	17 (50.0%)	0.259
Patients receiving atropine	3 (8.8%)	1 (3.0%)	2 (5.9%)	0.605
Hospital stays (d)	8.2±1.5	8.6±3. 0	8.9±2.5	0.458
Postoperative pain intensity at rest[a]				
Postoperative 4–6 h	3.32±0.38	3.40±0.36	3.34±0.37	0.984
Postoperative 24 h	1.86±0.30	2.12±0.29	1.85±0.28	0.708
Patients requiring rescue analgesics	5 (14.7%)	3 (9.1%)	1 (2.9%)	0.234

Notes: Values are mean ± SD, median (IQR), or number (proportion). [a]Postoperative pain intensity at rest assessed by an 11-point numeric rating scale (0, no pain; 10, worst pain imaginable) and analyzed by generalized linear model.
Abbreviations: LN, low-dose nalmefene 0.1 $\mu g \cdot kg^{-1}$; HN, high-dose nalmefene 0.25 $\mu g \cdot kg^{-1}$; C, control, normal saline; SD, standard deviation.

across all groups. At endotracheal intubation (T3) and skin incision (T4), the MAP in all groups increased significantly compared to after anesthesia induction (T2): (66.8 ± 10.8) vs (76.4 ± 17.7) at T3 and (82.9 ± 15.7) at T4 mmHg in Group C; (68.0 ± 12.0) vs (78.2 ± 15.3) at T3 and (80.1 ± 14.0) at T4 mmHg in Group LN; (68.6 ± 15.1) vs (78.1 ± 16.0) at T3 and (78.2 ± 12.2) at T4 mmHg in Group HN. Likewise, the HR at T3 was significantly higher than that at T2 among the groups: (65.2 ± 11.9) vs (66.9 ± 13.8) bpm in Group C; (61.0 ± 11.8) vs (67.8 ± 14.7) bpm in Group LN; (65.2 ± 11.7) vs (70.0 ± 14.5) BMP in Group HN.

Postoperative Pain Intensity and Side Effects

After adjusting for bias, there were no significant differences between the groups in terms of postoperative pain intensity (as measured by NRS scores at rest, at 4–6 h and at 24 h after surgery) and the number of patients requiring rescue analgesics (Table 2). Furthermore, the opioid-related side effects, including nausea, vomiting, drowsiness, dizziness, headache, shivering, fever, hypotension, urinary retention, and pruritus, were not significantly different among the three groups (Table 4).

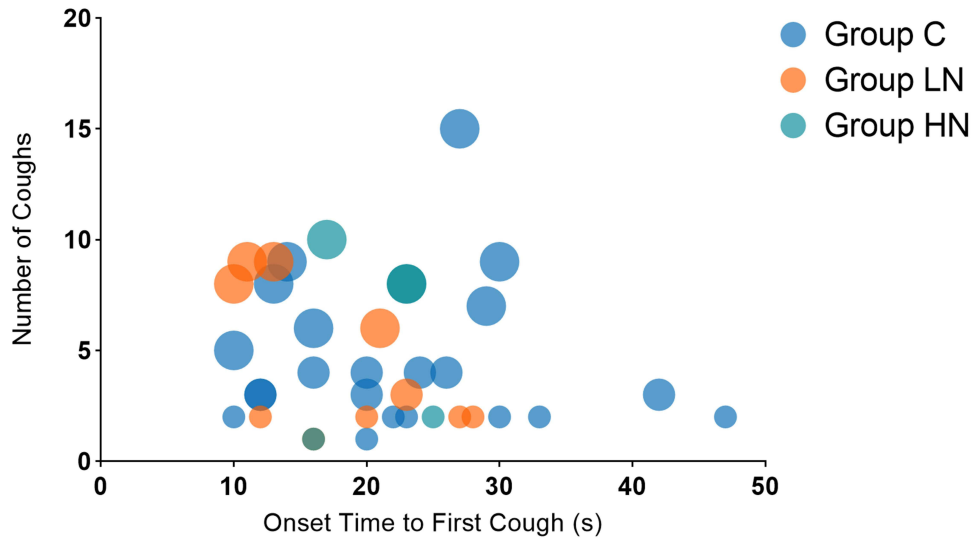

Figure 2 Bubble Plot. The Bubble Plot shows that SIC happened in more patients in Group C (number of bubbles), and the proportion of severe cough (dimension of bubbles) was significantly higher. Each circle represents a single patient with SIC. The dimension of each circle is the severity of SIC. The bigger the circle is, the more severe the SIC was.

Discussion

In this prospective clinical trial, patients undergoing breast surgery received an infusion of sufentanil (0.5 μg·kg^{-1}) within 2 s and tended to experience uncontrolled cough reflex. Our findings revealed that preadministration of nalmefene before induction of general anesthesia effectively inhibited SIC, reduced the relative risk of cough development, and alleviated the severity of the cough.

Different types of fentanyl analogs can induce coughs, although the incidence varies.[3,18] A variety of factors can contribute to the occurrence of fentanyl-induced cough, including both individual (eg, age,[19,20] sex, race, a history of smoking, or respiratory diseases) and medical factors (eg, dose or concentration of the drug,[21] types of fentanyl analogs, speed of intravenous injection,[22] or types of intravenous access).[23] Generally, old age, smoking, absence of a history of respiratory diseases, small doses and low concentrations of the drug, low speed of intravenous injection, and administration via the peripheral vein are associated with a lower incidence of triggered cough reflex after intravenous administration of fentanyl and related derivatives. In our trial, the incidence of SIC was as high as 64.7% when a high dose of sufentanil was rapidly injected into patients without any intervention. Our results were comparable to the findings of Sun et al,[4] who observed an incidence of 70% induced by an administration of equivalent fentanyl (5 μg·kg^{-1}) at the

Table 3 Characteristics of Sufentanil-Induced Cough

	Group C (n=34)	Group LN (n=33)	Group HN (n=34)	*P*
Incidence of SIC	22 (64.7%)	10 (30.3%)[a]	5 (14.7%)[a, b]	<0.001
Adjusted RR (95% CI)		0.466[a, c, e] (0.265–0.819)	0.241[a, b, d, e] (0.102–0.568)	
Number of SIC within 2 mins	2 (0–4)	0 (0–2)[a]	0 (0–0)[a, b]	<0.001
Severity of SIC				0.001
None of cough	12 (35.3%)	23 (69.7%)[a]	29 (85.3%)[a]	
Mild	7 (20.6%)	5 (15.2%)[a]	2 (5.9%)[a]	
Moderate	8 (23.5%)	1 (3.0%)[a]	0	
Severe	7 (20.6%)	4 (12.1%)[a]	3 (8.8%)[a]	
Onset time to first cough (s)	22.6±10.0	18.1±6.6	20.8±1.8	0.411

Notes: Values are number (proportion), median (IQR), or mean ± SD, [a]P<0.05 compared with Group C, [b]P>0.05 compared with Group LN, [c]P=0.008 compared with Group C, [d]P=0.001 compared with Group C, [e]Robust poisson regression model.
Abbreviations: SIC, Sufentanil-induced cough; RR, relative risk; LN, low-dose nalmefene 0.1 μg·kg^{-1}; HN, high-dose nalmefene 0.25 μg·kg^{-1}; C, control, normal saline; SD, standard deviation.

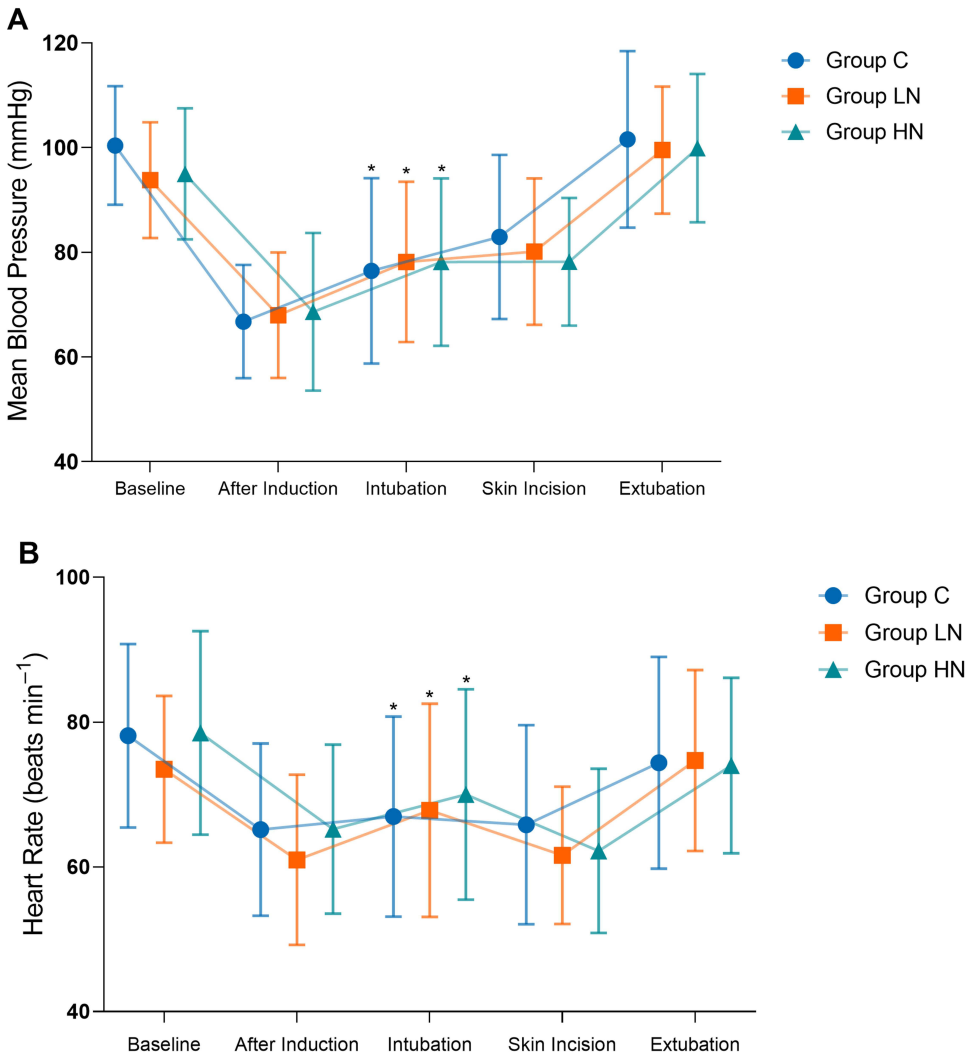

Figure 3 Time course of mean blood pressure (**A**) and heart rate (**B**) during intraoperative period. Values are mean ± SD. *Significant difference was observed compared with their respective values after induction.

same injection rate as in our study, and significantly higher than the findings of Lin et al[24] (31% induced by sufentanil 0.5 μg·kg^{-1} within 5 s) and Agarwal et al[3] (15% induced by sufentanil 0.3 μg·kg^{-1} within 5 s). To ensure an accurate evaluation, a robust Poisson regression model was used to adjust for bias.

Table 4 Postoperative Side Effects

	Group C (n=34)	Group LN (n=33)	Group HN (n=34)	*P*
Nausea	2 (5.9%)	3 (9.1%)	5 (14.7%)	0.468
Vomiting	6 (17.6%)	1 (3.0%)	4 (11.8%)	0.155
Drowsiness	2 (5.9%)	1 (3.0%)	0	0.360
Dizziness	7 (20.6%)	5 (15.2%)	3 (8.8%)	0.394
Headache	2 (5.9%)	2 (6.1%)	0	0.347
Shiver	1 (2.9%)	1 (3.0%)	2 (5.9%)	0.780
Fever	1 (2.9%)	1 (3.0%)	0	0.596
Hypotension	1 (2.9%)	0	0	0.370
Urinary retention	1 (2.9%)	0	0	0.370
Pruritus	0	0	0	–

Note: Values are number (proportion).
Abbreviations: LN, low-dose nalmefene 0.1 μg·kg^{-1}; HN, high-dose nalmefene 0.25 μg·kg^{-1}; C, control, normal saline.

In this study, the preadministration of nalmefene effectively inhibited SIC at either 0.1 or 0.25 μg·kg^{-1}. Preclinical models may implicate synergistic effects of different opioid receptors on the antitussive effects of nalmefene, although the mechanisms underlying the development of SIC are not fully understood. In contrast, the activation of rapidly adapting receptors (RARs), a kind of sensory receptor in airway vagal afferents, is triggered by the mechanical signals of bronchoconstriction due to the agonist effect of the mu2-opioid receptor.[10,25] The signal is then transmitted to the cough center in the medulla through the vagus nerve, causing coughs.[23,25,26] Once the mu2 opioid receptor is blocked by nalmefene, the cough reflex is depressed. In contrast, animal studies have shown that selective delta-opioid receptor antagonists suppress the capsaicin-induced cough reflex.[14] In addition, the inhibition of excitatory postsynaptic potentials in the nucleus tractus solitarius (NTS) due to the agonistic action of the kappa-opioid receptor, which also contributes to the antitussive effect of nalmefene.[27,28] Our findings indicate a decrease in the incidence and relative risk of SIC. To determine the optimal dose of nalmefene for preventing SIC, further studies are necessary.

In our study, nalmefene failed to reverse the analgesic effect of sufentanil, causing significant fluctuations in hemodynamics during intubation and/or skin incision. Previous studies have shown the minimum effective concentration of sufentanil as 0.2–0.3 μg·kg^{-1}. At this concentration, sufentanil inhibits the noxious stimuli response due to endotracheal intubation in both adults and children.[2,29,30] To obtain more accurate results, 0.5 μg·kg^{-1} sufentanil was used to induce SIC in our trial. Therefore, there was no significant clinical sign when nalmefene 0.1 μg·kg−1 or 0.25 μg·kg−1 antagonises sufentanil. Additionally, the synergistic antinociceptive effects of nalmefene could be a factor.[31,32] In vitro experiments showed that low concentrations of opioid receptor antagonists demonstrated selective antagonistic actions on excitatory opioid receptor functions in mouse dorsal root ganglion (DRG) neurons, thereby enhancing the antinociceptive potency of opioids.[33,34] In our postoperative follow-up, patients who received nalmefene did not report more severe postoperative pain intensity or an increase in postoperative side effects. Our results were consistent with findings in studies by Joshi et al[35] and Gan et al[36] Taken together, preadministration of nalmefene may be a good option for preventing SIC in the induction of general anesthesia.

This study had some limitations. First, the small sample size may have increased the risk of category II errors and may have overestimated the preventive effect of nalmefene on SIC. Second, the three different interventions used in this study may suggest that nalmefene is effective in suppressing the incidence and severity of SIC; however, the optimal dose of nalmefene for the prevention of SIC during the induction of general anesthesia requires further investigation. Finally, approximately 40% of breast surgery patients have persistent pain for up to one year after surgery, which is associated with nociceptive hyperalgesia due to central sensitization.[37,38] In contrast, studies have shown that opioid receptor antagonists can alleviate postoperative nociceptive hypersensitivity.[12] Our study only focused on short-term pain outcomes and failed to evaluate the clinical value of nalmefene in terms of long-term benefits for SIC.

Conclusions

An intravenous injection of sufentanil may lead to an uncontrolled cough reflex with a high incidence of 64.7%. We found that preadministration of nalmefene before induction of general anesthesia inhibited the SIC effectively, reduced the relative risk for the development of cough, and alleviated the severity of cough in patients undergoing breast surgery, without causing significant intraoperative hemodynamic fluctuations or increased postoperative pain intensity.

Abbreviations

SIC, sufentanil-induced cough; CONSORT, Consolidated Standards of Reporting Trials; ASA, American Society of Anesthesiologists; ACEI, angiotensin-converting enzyme inhibitors; ARB, angiotensin II receptor blockers; URTI, upper respiratory tract infection; COPD, chronic obstructive pulmonary disease; ECG, electrocardiogram; SPO_2, peripheral capillary oxygen saturation; NIBP, non-invasive blood pressure; HR, heart rate; MAC, minimal alveolar concentration; PONV, postoperative nausea and vomiting; NRS, numerical rating scale; SD, standard deviation; IQR, interquartile range; ANOVA, one-way analysis of variance; RR, relative risk; CI, confidence interval.

Data Sharing Statement

The datasets used and/or analyzed during the current study are available from the corresponding author upon reasonable request.

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Disclosure

The authors report no conflicts of interest in this work.

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