British Journal of Anaesthesia **105** (5): 661–7 (2010)
Advance Access publication 28 September 2010 · doi:10.1093/bja/aeq257

BJA

PAIN

Maintenance anaesthetics during remifentanil-based anaesthesia might affect postoperative pain control after breast cancer surgery‡

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Key points

- Sevoflurane anaesthesia under high remifentanil concentration induces remifentanil-induced hyperalgesia (RIH) compared with low remifentanil concentration.
- Propofol anaesthesia does not induce RIH regardless of the applied remifentanil concentration.
- Thus, propofol maintenance under remifentanil-based anaesthesia provides better analgesia by suppression of RIH than sevoflurane.

Background. Although remifentanil provides profound analgesia during operation, postoperative occurrence of hyperalgesia and tolerance after remifentanil administration could be a challenge to the postoperative pain control. In this investigation, we sought to determine the effect of maintenance with propofol or sevoflurane on postoperative analgesia after remifentanil-based anaesthesia.

Methods. Two hundred and fourteen women undergoing breast cancer surgery under remifentanil-based general anaesthesia were randomly included in this prospective and double-blind trial. The patients were anaesthetized with sevoflurane (S) or propofol (P) under high (H) or low (L) effect-site concentration (Ce) of remifentanil-based anaesthesia using a target-controlled infusion system; the patients were allocated into the SH, SL, PH, and PL groups. Pain intensity (visual analogue score, VAS) and cumulative morphine requirements were recorded 30 min, 1, 6, 12, and 24 h after operation.

Results. The patient characteristics were similar. Cumulative morphine consumption at 24 h after surgery was higher in the SH group [38.6 (SD 14.9)] compared with the SL [31.5 (3.7)], PH [31.7 (8.3)], and PL groups [30.1 (6.1)] ($P<0.001$). The VAS scores during 24 h after surgery were also higher in the SH group than the SL, PH, and PL groups ($P<0.001$).

Conclusions. Remifentanil hyperalgesia was induced by high dose of remifentanil-based anaesthesia during sevoflurane anaesthesia, whereas that was not apparent during propofol anaesthesia. Also, remifentanil hyperalgesia did not occur during low dose of remifentanil-based anaesthesia. Maintenance of propofol during high-dose remifentanil-based anaesthesia provided better postoperative analgesia.

Keywords: anaesthetics, i.v.; propofol, hyperalgesia, inhalation anaesthesia; sevoflurane, remifentanil

Accepted for publication: 6 July 2010

During general anaesthesia, opioids are commonly administered with either i.v. or inhaled hypnotic drugs. Remifentanil is widely used in clinical settings and as a useful supplement to general anaesthesia for several reasons, including its minimal alveolar concentration-reducing effects,[1] attenuation of the autonomic, somatic, and adrenocortical responses to noxious stimuli,[2–4] and rapid cognitive recovery.[5]

Nevertheless, remifentanil administration during anaesthesia has been associated with the frequent development of opioid-induced hyperalgesia due to its potent and short-acting properties.[6 7] Therefore, remifentanil-based anaesthesia could be a challenge for postoperative pain control.

The mechanism underlying opioid-associated hyperalgesia is still unclear, but a critical role has been attributed to an endogenous pain facilitatory system involving the *N*-methyl-D-aspartate (NMDA) receptor.[8–10] Recently, Zhao and Joo[11] demonstrated that clinically relevant concentrations of remifentanil induced rapid, persistent increases in NMDA responses that mirror the development of remifentanil-induced hyperalgesia. Several studies have demonstrated that i.v. or inhaled anaesthetics inhibit NMDA receptors and might modulate postoperative hyperalgesia.[12–15]

In the current study, we first examined whether high concentration of remifentanil could induce opioid-induced

†The first two authors contributed equally to this article.
‡This article is accompanied by the Editorial.

hyperalgesia. We then addressed the question of whether the choice of anaesthetics might have an influence on the postoperative pain control by modulating opioid-induced hyperalgesia. Therefore, the aim of this study was to evaluate and compare the influence of two maintenance anaesthetics, sevoflurane or propofol, on the intensity of postoperative pain in the clinical setting of possible occurrence of remifentanil-induced hyperalgesia, in patients undergoing breast cancer surgery.

Methods

This study was approved by the Institutional Review Board of the Pusan National University Hospital. After signed informed consent was obtained from the patients, 214 adult women aged between 20 and 65 yr with an ASA physical status of I or II undergoing elective breast cancer surgery were enrolled. Patients with neurological or psychiatric disorders, a history of drug abuse or chronic use of opioids or sedative drugs, obesity (BMI >30), the intake of any analgesic drug within 48 h before surgery, or poorly controlled hypertension were excluded. Pregnant patients were also excluded from the study. All patients accepted the use of patient-controlled analgesia (PCA) for perioperative pain control.

On the day before surgery, patients were instructed on how to use the PCA (Pain Management Provider, Abbott, USA) device and the visual analogue scale (VAS; 0, no pain; 10, worst pain imaginable). Patients were not allowed to have solid food or clear liquids after midnight on the day before surgery. All patients received midazolam 3 mg and glycopyrrolate 0.2 mg, i.m., 30 min before surgery. In the operating theatre, standard monitoring and bispectral index (BIS; Bispectral index™, Aspect Medical System, Norwood, MA, USA) monitoring were performed and baseline values were recorded. According to the method of anaesthetic induction and anaesthesia, the patients were randomly assigned, in a double-blinded manner, to one of the four groups. Randomization was done by two independent anaesthetists using 200 opaque-sealed envelopes, 50 for each group, indicating patient group assignment and describing the anaesthetic protocol for this particular group. The patients and anaesthetists involved in assessing postoperative pain, analgesic consumption, data collection, and analysis of results were not aware of group assignment.

In the propofol groups, anaesthesia was induced with continuous propofol and remifentanil (low or high dose) infusion by target-controlled infusion (TCI) (Orchestra® with Base Primea, Fresenius Kabi, France) to reach 4 μg ml^{-1} and 4 ng ml^{-1} (PH group) or 1 ng ml^{-1} (PL group) of target effect-site concentration (Ce). In sevoflurane subjects, anaesthesia was induced with thiopental 5 mg kg^{-1} and continuous remifentanil (low or high dose) infusion, using TCI to reach 4 ng ml^{-1} (SH group) or 1 ng ml^{-1} (SL group) of Ce. The pharmacokinetic sets used to calculate target effect-site concentrations of propofol and remifentanil were those published by Schnider and colleagues[16] and Minto and colleagues,[17] respectively.

Once the BIS scale was stable between 40 and 50, rocuronium 0.6 mg kg^{-1} was used to facilitate tracheal intubation. Anaesthesia was maintained according to the allocated group and a 1:1 mixture of oxygen and air. Mechanical ventilation was adjusted to maintain an end-tidal carbon dioxide concentration of 30–35 mm Hg throughout surgery using an anaesthetic/respiratory gas analyzer. Neuromuscular block was maintained via intermittent i.v. injection of rocuronium 0.2 mg kg^{-1}.

The BIS value was used to guide administration of propofol and sevoflurane. The target range of BIS during maintenance was 40–50. If the BIS value was not in a given range for at least 1 min or clinical signs of inadequate anaesthesia such as patient movement, coughing, tearing, or sweating were showed, we treated with increasing or decreasing Ce of propofol by 0.5 μg ml^{-1} increments or inspired concentration of sevoflurane by 0.5%. Mean arterial pressure (MAP) and heart rate (HR) were used to guide the administration of remifentanil. Both variables were maintained within 20% of baseline values, if hypotension (MAP <60 mm Hg) or bradycardia (HR <45 beats min^{-1}) occurred more than 5 min, the patient was treated with ephedrine 10 mg or atropine 0.5 mg. We excluded the case if the patient was administered ephedrine or atropine more than three times.

Thirty minutes before the end of surgery, morphine sulphate 2 mg was administered i.v., and background infusion of PCA was started. At the end of surgery, propofol, sevoflurane, and remifentanil were discontinued and ramosetron 0.3 mg was administered i.v. for antiemetic prophylaxis. Neuromuscular block was antagonized by combined i.v. glycopyrrolate (0.008 mg kg^{-1}) and pyridostigmine (0.2 mg kg^{-1}) at the completion of surgery. The same surgical and anaesthesia teams performed all the procedures. After recovery of adequate spontaneous ventilation and the obeisance to verbal commands such as eye opening, the tracheal tube was removed. The patients were transferred to the post-anaesthesia care unit (PACU), where standard monitoring was recorded every 15 min using the modified Aldrete score. An Aldrete score ≥9 and Sp_{O_2}>95% with oxygen 2 litre min^{-1} or >92% without oxygen signified recovery of physical, mental, and physiological function to near preanaesthetic levels. After discharge from the PACU, the patient was transferred to the general ward and the postoperative parameters were assessed.

The pain was controlled by PCA, which was programmed to deliver demand doses of morphine sulphate 1.0 mg with a 20 min lockout interval and continuous infusion of 1.0 mg h^{-1}. The 4 h limit of morphine sulphate was set to not exceed 20 mg. Pain intensity was assessed by the patients using VAS scale. If there was patient requirement or VAS scale was >5, the patient was administered morphine 4 mg i.v. as rescue analgesics. This PCA regimen was maintained in the PACU and the general ward.

Measurements

Baseline HR and MAP were defined as the mean of the two lowest measurements recorded during a 3–5 min interval

just before induction of anaesthesia. Values from all routine anaesthetic monitors were recorded at 5 min intervals during surgery. Duration of anaesthesia and surgery, the length of stay in the PACU, and the total doses of remifentanil given in the operating theatre were also recorded.

The cumulative consumption of morphine given by PCA and the pain intensity using the VAS were recorded at 30 min, 1, 6, 12, and 24 h after surgery. The primary outcome was the consumption of morphine during the first 24 h after surgery.

The degree of sedation was monitored by the Ricker sedation-agitation scale[18] on arrival in the PACU and 1 h after surgery. The incidence of postoperative nausea and vomiting (PONV; including all episodes of nausea, retching, and vomiting) and requirements for antiemetics were recorded within 24 h after surgery. Subjects who experienced vomiting or required antiemetic therapy within 24 h after surgery were given ondansetron 4 mg i.v. Other adverse events such as respiratory depression, muscular rigidity, or shivering were also recorded.

Statistical analysis

Age, weight, height, BMI, duration of surgery and anaesthesia, length of stay in the PACU, and intraoperative remifentanil consumption were analysed by one-way analysis of variance (ANOVA). Haemodynamic variables (MAP and HR), BIS scales, cumulative morphine consumption, and VAS scale were analysed by repeated-measures ANOVA for inter-group comparison. For *post hoc* comparisons, we used the Bonferroni test, as needed. The Ricker sedation-agitation scale was analysed by the Kruskal–Wallis test. The χ^2 test was used to compare the type of surgery, intraoperative atropine or ephedrine use, requirement for antiemetic drugs, and incidence of postoperative complications (PONV, respiratory depression, muscular rigidity, and shivering). The level of statistical significance was set at $P<0.05$. All analyses were performed using StatView version 5.0 (SAS, Chicago, IL, USA) and MedCalc® version 9.3.1 (MedCalc Software, Mariakerke, Belgium). An estimated sample size indicated that 41 patients per group would give a β-risk of 80% at an α-level of 0.05 for detecting a difference in morphine consumption of at least 5.0 mg at 24 h after the operation with a standard deviation of 8.0 for each group in the preliminary test.

Results

Two hundred and fourteen patients were enrolled, and 14 patients were excluded because of sudden refusal and unsuitability of the inclusion criteria. One hundred and eighty-six patients were analysed: 46 in Group PH, 50 in Group PL, 42 in Group SH, and 48 in Group SL due to intractable PONV and excess use of ephedrine of atropine (Fig. 1). All groups did not differ in patient characteristics among the groups (Table 1). Intraoperative remifentanil consumption was much higher in Groups PH and SH compared with Groups PL and SL; furthermore, intraoperative ephedrine and atropine uses were significantly higher in Group PH (37.0%) compared with Groups PL, SH, and SL ($P=0.009$, Table 2).

In the aspect of cumulative morphine consumption during the first 24 h after surgery, there was a significant difference between sevoflurane and propofol under high dose of remifentanil-based anaesthesia, whereas there was no difference between sevoflurane and propofol under low dose of remifentanil-based anaesthesia (Fig. 2A).

There was a significant difference between sevoflurane and propofol under high dose of remifentanil-based anaesthesia in the VAS scores, whereas there was no difference between sevoflurane and propofol under low dose of remifentanil-based anaesthesia. The VAS scores were significantly higher in Group SH than Groups PH and PL within 24 h after surgery, and the significant differences were observed at 30 min and 1 h after surgery (Fig. 2B).

MAP was higher and HR was slower in Group PL than in Group SL ($P=0.041$ and 0.001), whereas there were no significant differences between Groups PH and SH. BIS was similar among the groups.

The incidence of PONV was significantly lower in Group PL (18.0%) compared with Groups PH (43.5%), SH (45.2%), and SL (43.8%) ($P=0.013$). Consequently, the requirement for antiemetic drugs was higher in Groups PH and SH than in Groups PL and SL ($P=0.005$). The incidence of shivering was also significantly higher in Groups PH and SH than in Groups PL and SL ($P=0.004$). The Ricker sedation-agitation scales were in the range of 3–5 for all patients, and it was possible to determine VAS. There were no significant differences in the degree of sedation among the groups ($P=0.099$, Table 3). Other adverse events including respiratory depression and muscular rigidity were not shown.

Discussion

Our results showed that the maintenance of sevoflurane provided high morphine consumption and higher VAS scores after breast cancer surgery compared with the maintenance of propofol under high dose of remifentanil-based anaesthesia, not under low dose of remifentanil-based anaesthesia. Group SH reported greater cumulative morphine consumption during the first 24 h than Group SL, which could be a strong predictor of occurrence of remifentanil-induced hyperalgesia. In contrast, Group PH reports similar cumulative morphine consumption or VAS scores compared with Group PL. These findings suggest that maintenance of propofol in remifentanil-based anaesthesia provides better postoperative analgesia by suppression of remifentanil-induced hyperalgesia.

Several studies suggested that acute and chronic exposure to opioids can be associated with the development of hyperalgesia and NMDA receptor involved in the genesis of opioid-associated hyperalgesia by pain-facilitating system.[19] Remifentanil supplementation during anaesthesia is known to be associated with the occurrence of the opioid-induced hyperalgesia; this is clinically significant, because large doses of intraoperative μ-opioid receptor agonists can increase

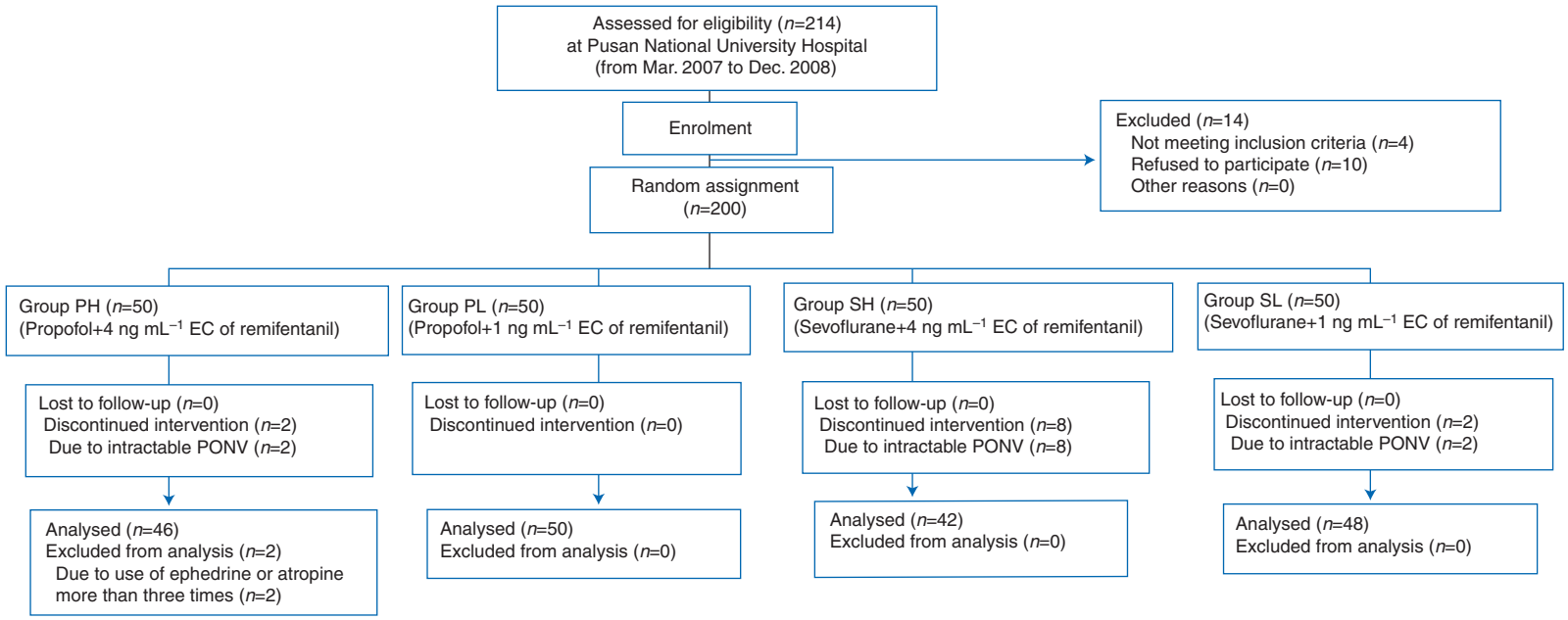

Fig 1 Consort flow diagram.

Table 1 Patient characteristic data and types of surgery in each group. Values are mean (range), mean (SD), or number (%). Group PH, propofol+4 ng ml^{-1} Ce of remifentanil; Group PL, propofol+1 ng ml^{-1} Ce of remifentanil; Group SH, sevoflurane+4 ng ml^{-1} Ce of remifentanil; and Group SL, sevoflurane+1 ng ml^{-1} Ce of remifentanil. Ce, effect-site concentration

Variables	Group PH (n=46)	Group PL (n=50)	Group SH (n=42)	Group SL (n=48)	P-value
Age (yr)	50.4 (27–65)	47.8 (35–62)	50.2 (33–64)	47.0 (33–63)	0.147
Weight (kg)	58.9 (9.6)	57.6 (7.3)	59.4 (8.5)	57.3 (4.6)	0.490
Height (cm)	157.4 (5.1)	158.7 (4.9)	158.7 (4.9)	158.6 (4.8)	0.528
BMI (kg m^{-2})	22.7 (2.0)	22.9 (3.1)	22.7 (2.1)	22.8 (2.0)	0.977
Types of surgery					
Mastectomy/s flap surgery	16 (34.8)	18 (36.0)	13 (31.0)	16 (33.3)	0.999
Mastectomy/c local flap	10 (21.7)	12 (24.0)	10 (23.8)	11 (22.9)	
Mastectomy/c latissimus dorsi flap	20 (43.5)	20 (40.0)	19 (45.2)	21 (43.8)	
Duration of surgery (min)	193.6 (70.3)	207.0 (92.9)	208.8 (70.3)	222.0 (72.4)	0.389
Duration of anaesthesia (min)	231.1 (72.3)	219.2 (94.4)	235.6 (79.0)	243.5 (74.2)	0.514
Length of stay in PACU (min)	36.3 (12.6)	40.2 (18.5)	37.9 (8.9)	41.8 (16.9)	0.294

Table 2 Intraoperative consumption of remifentanil, ephedrine, or atropine in each group. Values are mean (SD) or number (%). Group PH, propofol+4 ng ml^{-1} Ce of remifentanil; Group PL, propofol+1 ng ml^{-1} Ce of remifentanil; Group SH, sevoflurane+4 ng ml^{-1} Ce of remifentanil; and Group SL, sevoflurane+1 ng ml^{-1} Ce of remifentanil. $^{\dagger}P<0.05$ compared with SL; $^{\ddagger}P<0.05$ compared with PL. PACU, post-anaesthetic care unit; Ce, effect-site concentration

Variables	Group PH (n=46)	Group PL (n=50)	Group SH (n=42)	Group SL (n=48)	P-value
Remifentanil consumption (μg)	2064.3 (680.9)†,‡	762.5 (422.1)	2070.9 (726.0)†,‡	870.3 (387.3)	<0.001
Ephedrine or atropine use	17 (37.0)‡	6 (12.0)	12 (28.6)	8 (16.7)	0.017

postoperative pain and morphine consumption.[7] More recently, Zhao and Joo[11] presented a cellular mechanism involving the rapid and prolonged up-regulation of NMDA receptor function by remifentanil, which may contribute to the clinical development of remifentanil-induced hyperalgesia. As expected, in sevoflurane groups, we observed that the large dose of remifentanil caused hyperalgesic responses whereas those responses were not exhibited in the small dose of remifentanil.

In the past, several investigators suggested that there was no difference in postoperative matters between propofol and inhalation anaesthetics,[20 21] thus the importance of the choice of maintenance hypnotics was overlooked. They did not conduct remifentanil-based anaesthesia, thus their study was not sufficient to confirm the effect of hypnotics on analgesia after opioid supplementation. Several observations suggested that propofol inhibits the NMDA subtype of the glutamate receptor.[12 15]

In a study of the effect of propofol on remifentanil-induced hyperalgesia, clinically relevant interactions of propofol and remifentanil existed, and propofol could delay and weaken remifentanil-induced hyperalgesia.[22] Recently, Cheng and colleagues[23] showed that propofol anaesthesia in fentanyl-based anaesthesia was associated with less postoperative pain than isoflurane anaesthesia, showing a similar conclusion to this study. The effects of sevoflurane on remifentanil-induced hyperalgesia have not yet been fully evaluated. Some studies have demonstrated that sevoflurane antagonizes the NMDA receptor in a dose-dependent manner.[13 24] A more recent study[25] suggested that, at clinical concentrations, the anti-hyperalgesic properties of sevoflurane are not sufficiently potent to prevent hyperalgesia induced by both nociceptive inputs and high doses of fentanyl.

This study was designed to assess whether the remifentanil-induced hyperalgesia or tolerance would occur in clinical settings and whether there would be difference in suppression of the hyperalgesia or tolerance depends on the maintenance anaesthetics. We confirmed that maintenance of propofol in remifentanil-based anaesthesia abolished the occurrence of hyperalgesia observed after maintenance of sevoflurane. The explanation for our results could be related to the pharmacokinetic differences between propofol infusion and sevoflurane inhalation. In this study, we did not measure the subanaesthetic concentrations in both groups. Previous studies demonstrated that propofol has an analgesic action at subhypnotic doses.[26 27]

On the other hand, the halogenous anaesthetics have been known for producing antianalgesia at subanaesthetic concentrations, with a maximal effect at ~1/10th the concentration required for anaesthesia.[28] Therefore, we could not exclude the effect of residual sevoflurane and the combined pharmacokinetic action between sevoflurane and remifentanil on postoperative hyperalgesia expressed in the SH group. In this study, although we demonstrated that propofol provided more benefit in the aspect of post-anaesthetic recovery, the difference in morphine consumption and VAS scale might not be an important matter clinically.

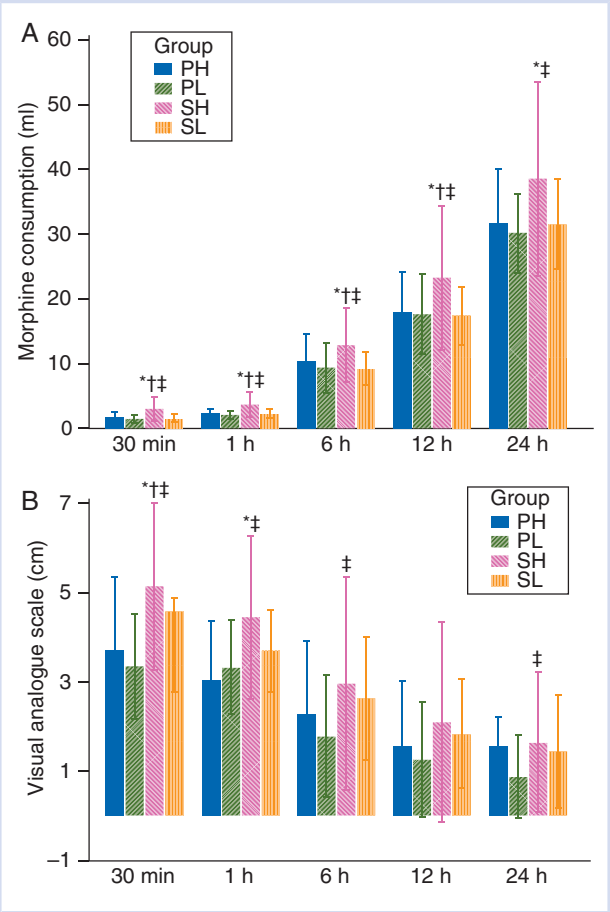

Fig 2 Cumulative morphine consumption (A) and VAS (B) during the first 24 h after surgery. Group PH, propofol+4 ng ml^{-1} Ce of remifentanil; Group PL, propofol+1 ng ml^{-1} Ce of remifentanil; Group SH, sevoflurane+4 ng ml^{-1} Ce of remifentanil; and Group SL, sevoflurane+1 ng ml^{-1} Ce of remifentanil. *$P<0.05$ compared with PH; †$P<0.05$ compared with SL; ‡$P<0.05$ compared with PL. Ce, effect-site concentration.

The PONV incidence is more than 75% without antiemetic prophylaxis in breast cancer surgical patients.[29] Although all the enrolled patients were given ramosetron in this study, the beneficial effects of propofol on PONV were attenuated during high dose of remifentanil infusion; those effects were shown only in the PL group. The incidence of postoperative shivering was much higher in high dose of remifentanil-based anaesthesia group. Thus, we assumed that the consumption of remifentanil might be a strong modulating factor of PONV and postoperative shivering in our study. As the sample size calculation was based on postoperative morphine consumption by PCA, the lack of differences in other variables may be attributed to a lack of power.

We have demonstrated that the maintenance of propofol during high dose of remifentanil-based anaesthesia led to better postoperative pain control compared with the maintenance of sevoflurane after breast cancer surgery. The reduction of postoperative pain was manifested as a decrease in morphine consumption and the VAS scale during the first 24 h after surgery. Thus, it could be assumed that propofol might have a more potent NMDA antagonism effect on the hyperalgesia elicited by remifentanil usage than that of sevoflurane. Although the use of propofol decreased the incidence of PONV during low dose of remifentanil infusion, there was no benefit on PONV and shivering under high dose of remifentanil-based anaesthesia.

There are several limitations in this study. The first limitation is that the beneficial effects of propofol were not translated into shortening of PACU stay. We assumed that the length of PACU stay in this study might be more dependent on the hospital facility and policy, not on the drug effect. As a second limitation, the usage of background infusion and long lockout interval might decrease the sensitivity of morphine consumption during the observation period.

In conclusion, our results suggest that maintenance of general anaesthesia by propofol may prevent remifentanil-induced hyperalgesia induced by high dose of remifentanil usage. Furthermore, propofol has the potential to reduce postoperative pain and hyperalgesia, although the combined use of propofol with high dose of remifentanil could induce the need for inotropic treatment compared with sevoflurane. A reduction in postoperative pain and morphine consumption might lead to earlier mobilization and earlier hospital discharge.

Conflict of interest

None declared.

Table 3 Comparisons of adverse effects. Values are number of patients (proportion) and median (lowest to highest value). Group PH, propofol+4 ng ml^{-1} Ce of remifentanil; Group PL, propofol+1 ng ml^{-1} Ce of remifentanil; Group SH, sevoflurane+4 ng ml^{-1} Ce of remifentanil; and Group SL, sevoflurane+1 ng ml^{-1} Ce of remifentanil. †$P<0.05$ compared with SL; ‡$P<0.05$ compared with PL. PONV, postoperative nausea and vomiting; Ce, effect-site concentration

Variables		Group PH ($n=46$)	Group PL ($n=50$)	Group SH ($n=42$)	Group SL ($n=48$)	P-value
PONV	0–24 h	20 (43.5)‡	9 (18.0)	19 (45.2)‡	21 (43.8)‡	0.013
Requirement for antiemetic drugs	0–24 h	10 (21.7)‡	2 (4.0)	12 (28.6)†,‡	5 (10.4)	0.005
Shivering	0–1 h	23 (50.0)†,‡	12 (24.0)	17 (40.5)†,‡	9 (18.8)	0.004
Ricker sedation-agitation scale	On recovery	3.6 (3–5)	3.6 (2–4)	3.9 (3–5)	3.7 (3–4)	0.890
	1 h	4.0 (4–4)	4.0 (4–4)	4.0 (4–4)	4.0 (3–4)	0.980

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