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SHORT COMMUNICATION

Effect of remifentanil on postoperative nausea and vomiting: a randomized pilot study

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Abstract

Opioid-related postoperative nausea and vomiting should not occur following remifentanil administration because of its relatively short time to elimination. However, studies have indicated that the incidence of postoperative nausea and vomiting associated with remifentanil is similar to that with other opioids. Hence, we aimed to determine whether intraoperative remifentanil itself is associated with postoperative nausea and vomiting when postoperative pain is managed without opioid use. In this prospective pilot study, 150 patients who underwent unilateral upper limb surgery under general anesthesia with brachial plexus block were included. Patients in the remifentanil and control groups received 0.5 μg/kg/min remifentanil and saline, respectively. Postoperative pain was managed using a brachial plexus block, non-steroidal anti-inflammatory drugs, and acetaminophen. The presence of postoperative nausea and vomiting within the first 24 h after anesthesia was assessed by an evaluator blinded to patient allocation. Eight patients were excluded from the final analysis, resulting in 72 and 70 patients in the remifentanil and control groups, respectively. Postoperative nausea and vomiting within 24 h after surgery occurred in 11 and 9 patients in the remifentanil and control groups, respectively. These data suggest that remifentanil use only minimally affects the incidence of postoperative nausea and vomiting under sevoflurane anesthesia.
UMIN Clinical Trials Registry identification number: UMIN000016110.

Keywords Remifentanil · Postoperative nausea and vomiting · Pilot study

Postoperative nausea and vomiting (PONV) are common and distressing. Residual opioids during surgery may cause PONV [1]. Hence, it is believed that remifentanil, which has a relatively short time to elimination, [2] should not cause PONV. However, studies have reported that the incidence of PONV for remifentanil is like that for other opioids [3–6].

The previous reports have few limitations. First, these studies utilized other opioids for postoperative pain management. Second, they included cases involving various operations, for example, abdominal surgery, which itself is a risk factor for PONV [3]. Moreover, anesthetics affecting PONV were used. To investigate the association of intraoperative remifentanil with PONV, it is necessary to exclude patients administered other perioperative opioids, and cases involving surgical procedures or anesthetics that influence PONV.

In this study, we aimed to determine whether intraoperative remifentanil itself is associated with PONV. To address the aforementioned problems, we selected patients undergoing upper limb surgery under general anesthesia, because postoperative pain following upper limb surgery can be managed almost entirely via brachial plexus block (BPB) and non-steroidal anti-inflammatory drugs (NSAIDs), without opioids. Additionally, upper limb surgery itself is not a risk factor for PONV [3]. Because it is difficult to avoid anesthetics in humans because of ethical concerns, sevoflurane was used in this study.

As there are no reports on the frequency of PONV with sevoflurane, we conducted a pilot study to assess its incidence in certain conditions in specific patients.

This study was approved by the Ethics Committee of Niigata Hand Surgery Foundation Hospital (Niigata, Japan) and registered in the UMIN Clinical Trials Registry (UMIN000016110) before the first participant was enrolled.

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The present study included 150 consecutive adult patients who underwent unilateral upper limb surgery under general anesthesia between January 2015 and November 2017. All patients provided written informed consent for participation. Patients who used preoperative antiemetics or opioids were excluded. Patients were randomly assigned to either the remifentanil or control group. Randomization was accomplished using a computer-generated randomization sequence (http://www.randomization.com), in blocks of 50. The nurse or pharmacist kept the randomization allocation table throughout the study. Patients and observers were blinded to group assignment throughout the study.

All patients received a combination of general anesthesia and brachial plexus block. After intravenous injection of atropine (0.5 mg), general anesthesia was induced using propofol (1.0–1.5 mg/kg) and rocuronium (initial dose of 0.6 mg/kg, followed by continuous administration at 5 μg/kg/min) for prevention of laryngeal spasm. General anesthesia was maintained using sevoflurane (end-expiratory sevoflurane concentration: 1.3% ± 0.1%) without nitrous oxide. In all cases, airway management was performed using a ProSeal™ Laryngeal Mask Airway (PLMA; Intavent-Orthofix, Maidenhead, UK) and positive pressure ventilation was performed with oxygen in air (FiO_2 0.4) using a semiclosed system to maintain normocapnia, and a 14-Fr stomach tube was inserted via the port of the PLMA. Brachial plexus blocks were performed via ultrasound-guided supraclavicular or infraclavicular approach using 1% mepivacaine (15 ml) and 0.75% ropivacaine (15 ml) after induction of general anesthesia. Patients undergoing surgeries that were more likely to induce intense postoperative pain [7] received ropivacaine (6–12 mg/h) for continuous peripheral nerve blockade.

Patients in the remifentanil group underwent continuous administration of remifentanil (0.5 μg/kg/min), while those in the control group underwent continuous administration of saline (0.3 ml/kg/h).

Ephedrine was administered at a dose of 4–8 mg when systolic blood pressure dropped below 80 mmHg. Immediately after the end of surgery, remifentanil or saline and rocuronium infusion was ceased, sevoflurane was exhausted using artificial respiration, and 2–4 mg/kg of sugammadex was administered to reverse neuromuscular blockade based on train of four values. After emergence from anesthesia and confirmation that the respiratory rate was 8 cycles/min or more and SpO_2 was 96% or more with O_2 3 l, the patients were moved to wards.

Postoperative administration of regular loxoprofen (60 mg) was initiated once oral ingestion became possible. If insufficient for pain control, other non-steroidal anti-inflammatory drugs (25 mg or 50 mg of diclofenac suppository, or 50 mg of flurbiprofen axetil) or 1000 mg of acetaminophen were administered; if still insufficient, pentazocine (15 mg or 30 mg) was administered. However, patients administered pentazocine were excluded from the analysis. If patients complained of nausea and requested relief, metoclopramide (10 mg) was administered.

Patients were assessed by evaluators blinded to patient allocation, at 0–0.5 h, 0.5–1 h, 1–1.5 h, 1.5–2 h, 2–6 h, 6–12 h, and 12–24 h after moving to a ward. Nausea was assessed by asking the patients about the presence of nausea or retching. PONV was defined as presence of nausea, retching, or vomiting, or request for antiemetics. The primary endpoint was the incidence of PONV within 24 h after moving to a ward. Secondary endpoints were the numbers of patients with PONV at each observation time and other adverse events associated with the use of remifentanil during surgery, respiratory rate on leaving the operating room, incidence of postoperative shivering, intraoperative blood pressure, pulse rate, and ephedrine usage.

As this is a pilot study, we did not calculate the sample size. We calculated the incidence rates with 95% confidence intervals (CIs) using GraphPad QuickCalcs (http://graphpad.com/quickcalcs/confInterval1/; GraphPad Software, Inc., San Diego, CA, USA) and the risk ratio using StatView (SAS Institute Inc., Cary, USA). We used Mann–Whitney *U* tests and Fisher's exact probability test to evaluate differences in the patient background and incidence rates of PONV and other adverse events, using StatView.

In total, 153 patients were assessed for eligibility; 150 patients were enrolled, who obtained complete anesthesia in the upper limb on which BPB had been performed when they emerged from general anesthesia; therefore, all blocks were considered successful. 8 of these 150 patients were excluded from the analysis. Thus, we analyzed data from 72 to 70 patients in the remifentanil and control groups, respectively (Fig. 1). No significant differences existed in patient background characteristics, including PONV risk factors (Table 1).

11 patients in the remifentanil group and 9 patients in the control group experienced PONV within 24 h after moving to a ward, resulting in incidence rates of 15.3% (95% CI 8.6–25.5) and 12.9% (95% CI 6.7–22.9), respectively. The risk ratio for the remifentanil group versus the control group was 1.22 (95% CI 0.47–3.16). Among the patients experiencing PONV, two in the remifentanil group and none in the control group requested metoclopramide ($p = 0.48$). Moreover, vomiting was observed in two cases in the remifentanil group and one case in the control group ($p > 0.99$). These findings indicate that the PONV incidence was slightly higher in the remifentanil group; however, remifentanil use alone minimally affected the PONV incidence under sevoflurane anesthesia.

The timing of PONV occurrence in each case is shown in Fig. 2. 7 of 11 patients (63.4%) in the remifentanil group and 4 of 9 (44.4%) in the control group reported early-phase PONV (0–2 h after moving to a ward; $p = 0.65$), while 5 in

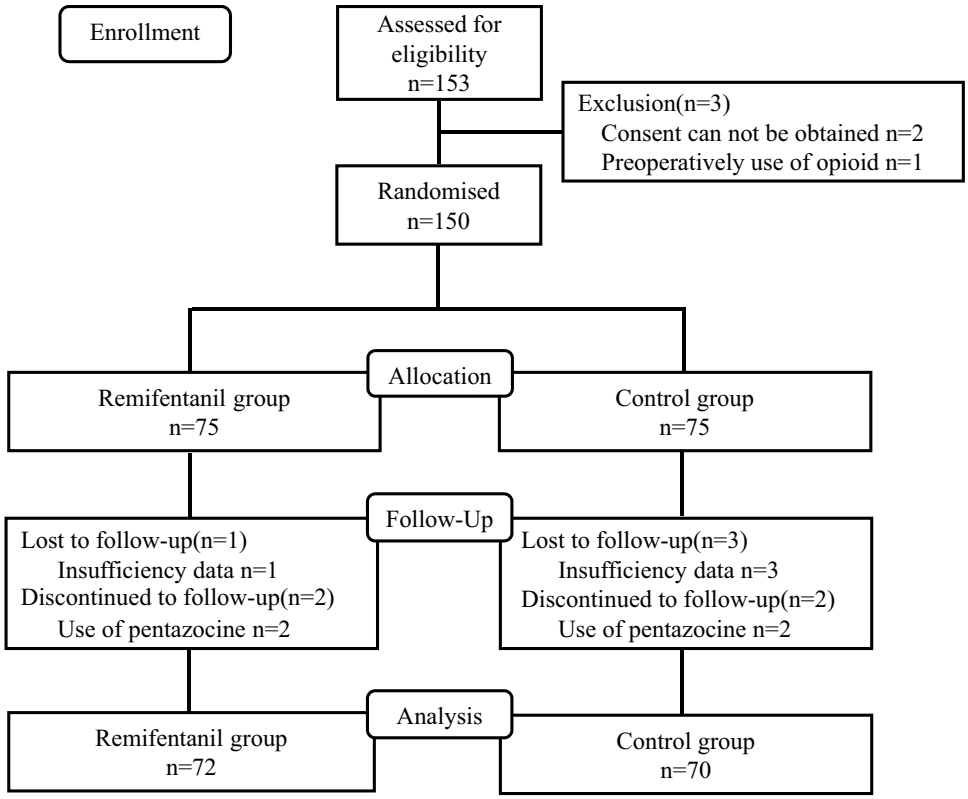

Fig. 1 CONSORT diagram showing the process of patient enrolment and subsequent analysis

Table 1 Patient background

	Group R ($n=72$)	Group C ($n=70$)	p value
Age (year)	51.8 ± 14.8	55.3 ± 16.6	0.36
Sex (M/F)	40/32	36/34	0.74
Height (cm)	163.1 ± 8.9	161.8 ± 10.6	0.47
Weight (kg)	62.6 ± 12.3	62.5 ± 12.4	0.80
BMI	23.5 ± 4.0	23.7 ± 3.3	0.86
Apfel score (0/1/2/3)	16/19/30/7	17/22/22/9	0.63
CBPB (Y/N)	31/41	31/39	> 0.99
Surgery time	70.3 ± 36.1	68.5 ± 36.2	0.79
Anesthetic time	122.9 ± 40.3	114.7 ± 39.2	0.29
Dose of sevoflurane (ml)	29.1 ± 9.8	29.0 ± 9.6	0.97
Dose of remifentanil (mg)	3.16 ± 1.48	0	< 0.01

BMI body mass index, *CBPB* continuous brachial plexus block

each group reported late-phase PONV (2–24 h after moving to a ward; $p > 0.99$).

Other adverse events (respiratory rate on leaving the operating room, postoperative shivering, intraoperative blood pressure, pulse rate, and ephedrine usage) are shown in Table 2.

Our findings indicated that remifentanil (0.5 μg/kg/min) minimally affected the PONV incidence under sevoflurane anesthesia for patients whose postoperative pain following upper limb surgery was managed without opioid use.

However, we observed a non-significant increase in the PONV incidence in the early phase (0–2 h). It is suggested that remifentanil remains in the system after awakening, because the respiratory rate on leaving the operating room was lower in the remifentanil group. Contrastingly, studies have revealed that the main risk factor for nausea in the early phase is not opioids but anesthetic inhalation [8]; therefore, sevoflurane was likely the main cause of early-phase PONV in the present study. As mentioned above, we observed that the respiratory rate was lower in the remifentanil than in the control group on leaving the operating room. This might have caused delayed excretion of sevoflurane, inducing PONV.

Although a previous study reported a PONV incidence of 20–30%, [9] in this study, the incidence was less (remifentanil group, 15.3% and saline group, 12.9%). The previous study, however, included cases involving surgeries that were PONV risk factors, including abdominal surgery, and cases in which opioids other than remifentanil were used in the perioperative period. The upper limb surgery is not a risk factor for PONV [3] and the patients were not administered any opioids other than remifentanil in this study.

The present study has several limitations. This was a pilot study. A pilot study does not provide a meaningful effect size estimate for planning subsequent studies, owing

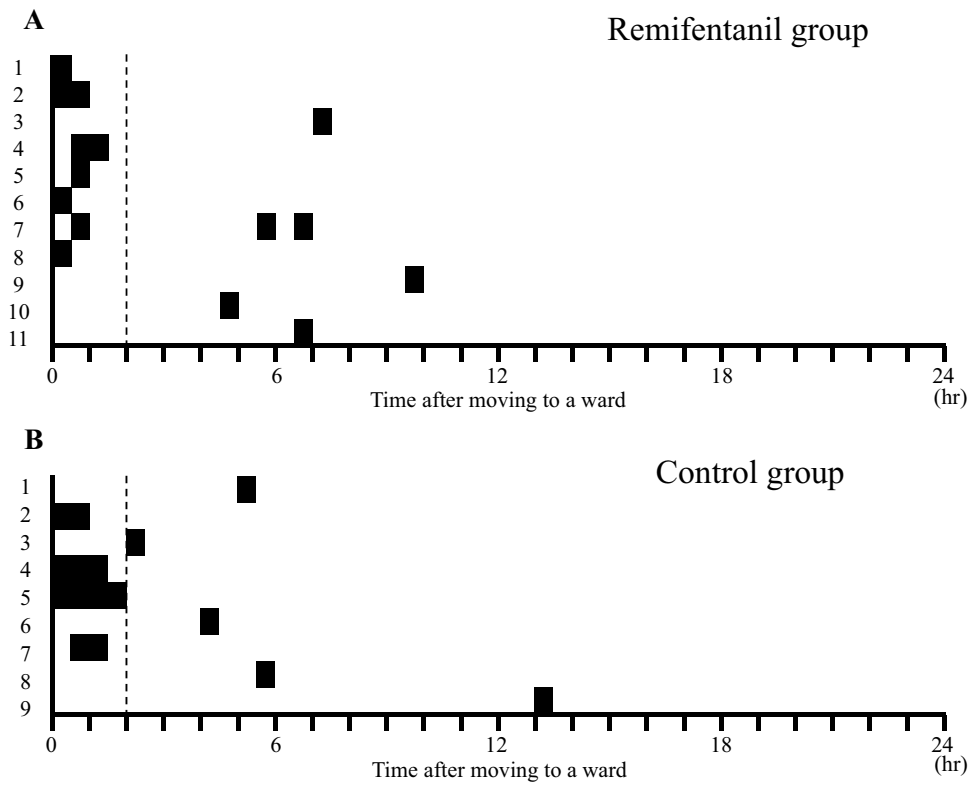

Fig. 2 Timing of PONV occurrence in each case. The dotted line separates the early and late phases. 7 of 11 patients (63.4%) in the remifentanil group and 4 of 9 patients in the control group reported PONV within 0–2 h of surgery. There were five cases of PONV in the late phase (2–24 h) in each group. *PONV* postoperative nausea and vomiting

Table 2 Other adverse events

	Group R ($n=72$)	Group C ($n=70$)	p value
Shivering (%)	4.2%	0%	<0.01
SBP (mmHg) (preoperative value)	160 ± 23	162 ± 21	0.52
SBP (mmHg) (intraoperative lowest value)	78 ± 9.0	98 ± 15	<0.01
HR (bpm) (preoperative value)	72 ± 14	71 ± 12	0.82
HR (bpm) (intraoperative lowest value)	60 ± 10	69 ± 11	<0.01
Rates of ephedrine use (%)	70.8%	14.3%	<0.01
Respiratory rates (cycles/min)	9.3 ± 2.3	15.3 ± 3.3	<0.01

SBP systolic blood pressure, *HR* heart rate

to the imprecision inherent in data from small samples [10]. Moreover, we used volatile anesthetics to maintain anesthesia. Anesthetics, not only volatile anesthetics but also propofol, affect PONV; volatile anesthetics have an emetic effect, [8] whereas propofol has an antiemetic effect [9]. The most accurate results would be obtained by examining the use of remifentanil without anesthetics; however, this is difficult because of ethical concerns. Although it is possible that their effects masked those of remifentanil, the influence was minimized by using anesthetics equally in both groups. Moreover, ephedrine is reported to reduce PONV. However, it was reported that this effect appeared when administered intramuscularly 10 min before the end of the procedure [11]. In this study, it might not cause an antiemetic effect post-surgery, because it was used only intravenously during surgery.

In conclusion, although the PONV incidence was slightly higher in the remifentanil group, our results suggest that remifentanil only minimally affects the PONV incidence under sevoflurane anesthesia. Based on the present findings, further research is needed.

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Compliance with ethical standards

Conflict of interest The author(s) declare that they have no conflict of interest.

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