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CLINICAL TRIAL REPORT

Effect of High Maintenance Dose Versus Low Dose of Remifentanil on Incidence of Postoperative Nausea and Vomiting (PONV) in Patients Under Gynecological Laparoscopic Procedure: A Pilot Study

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Purpose: The aim of this trial was to investigate postoperative nausea and vomiting (PONV) incidence between low- and high-dose remifentanil with propofol for total intravenous anaesthesia (TIVA) in adult female patients with gynecologic laparoscopy.

Patients and Methods: The randomized clinical trial consisted of two groups: 0.1ug/kg/min remifentanil (L group) (n=39) and 0.4ug/kg/min remifentanil (H group) (n=40). Both of them was titrated with propofol to maintain bispectral index (BIS) values between 40 and 60. Forty-eight-hour PONV and postoperative visual analogue scale (VAS) and haemodynamic parameters and recovery quality and the concentrations of propofol TCI during the intraoperative periods were evaluated.

Results: PONV incidences at 2, 6, 24, and 48 hours were 12.5%, 15%, 20% and 20% in (H group) and 25.6%, 25.6%, 25.6%, and 25.6% in (L group), but no statistical difference between groups (all P values > 0.05). H group reduced propofol use and recovery time (6.5 ± 4.8 versus. 8.7 ± 4.4 P = 0.036) but increased norepinephrine requirements (0 (0, 8) vs 0 (0, 0) P = 0.005). PCA use and first analgesic request time were similar.

Conclusion: High-dose remifentanil regimens for TIVA would not increase the incidence of PONV, however, significantly reduce the demand for propofol, and promote rapid recovery of patients.

Keywords: high-dose remifentanil, propofol, postoperative nausea and vomiting, PONV, hyperalgesia, bispectral index, BIS

Introduction

Postoperative nausea and vomiting (PONV) is a common perioperative adverse reaction with an incidence rate of 18%–50%. If not treated promptly, it can lead to various severe complications, thereby increasing medical costs and reducing patient satisfaction.[1] Previous studies have identified high-risk patients towards PONV, including female sex, non-smoking status, use of inhalation anaesthetics, and pneumoperitoneum.[2] Perioperative opioid use is considered a primary risk factor for PONV, with studies suggesting a correlation between the dosage of opioids, including morphine and fentanyl and its derivatives, and the occurrence and severity of PONV.[3] Remifentanil, a short-acting opioid, is widely used in TIVA due to its unique pharmacokinetic properties, allowing for a reduced dosage of other anaesthetics while achieving stable anaesthesia depth and haemodynamics and shortening the time for awakening, extubation, and PACU stay.[4] Meanwhile, high doses of remifentanil alone have been reported to significantly induce nausea and vomiting.[5] Its

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combined use with propofol anaesthesia and the resulting increase in PONV incidence remain controversial. Some scholars believe high doses of remifentanil increase the risk of PONV.[6] However, some scholars indicate that high-dose remifentanil TIVA does not increase PONV incidence and maintains comparable postoperative pain levels. Notably, the high-dose group showed stable BIS values during tracheal intubation, contrasting with significant BIS elevation in the low-dose group.[7] Furthermore, there is debate regarding whether high-dose remifentanil increases the risk of opioid-induced hyperalgesia (OIH).[8,9] Studies suggest that remifentanil increased postoperative pain and analgesic requirements, although it may induce hyperalgesic.[10] Opinions also differ on its effect on the BIS. Toshiya proposes that remifentanil exhibits inherent sedative-hypnotic properties, potentially potentiating propofol's hypnotic effects with consequent BIS alterations,[11] whereas Dahye Jung suggests it reduces burst suppression ratio in propofol-induced consciousness-disordered patients without significant BIS impact.[12] Nevertheless, current evidence remains inconclusive regarding whether high-dose remifentanil exacerbates PONV incidence, particularly in gynecologic laparoscopic patients who inherently belong to the PONV high-risk population. Furthermore, the association between high-dose remifentanil and postoperative hyperalgesia and BIS remains underexplored, especially in gynecologic laparoscopic surgery. This study primarily aimed to investigate whether high-dose remifentanil under propofol-based TIVA increases the incidence of PONV during gynaecological laparoscopy, with secondary objectives including evaluation of postoperative hyperalgesia incidence.

Materials and Methods

This prospective, double-blind, single-centre, parallel-group, randomized controlled trial was approved by the Ethics Committee of the First Affiliated Hospital of Zhejiang Chinese Medical University (protocol number: 2020-KL-038-03). Our study complies with the Declaration of Helsinki and registered at https://clinicaltrials.gov (protocol number: ChiCTR2300070104). For five months, 80 patients who underwent elective laparoscopic myomectomy, with cases classified as ASA I–II, were recruited after written informed consent was obtained. To ensure uniform surgical incisions across patients, they were randomly assigned to either the high-dose remifentanil group (H group) or the low-dose remifentanil group (L group), with 40 patients in each group. The exclusion criteria included the following: patients aged <20 or ≥60 years; those with malignant tumours, chronic pain and analgesic drug use; those with allergies to soybean oil or eggs; those with diabetes, coronary heart disease, severe liver or kidney dysfunction; smokers; those with Hb <10 g/L; those who had taken steroids, opioids, antihistamines, or antiemetic drugs within a month before surgery; and those with a body mass index (BMI) ≥25 or <18. Patients were randomly assigned at a 1:1 ratio by an assistant not involved in the study using computer-generated random sequences and the sealed envelope method. On the day of surgery, the patients were transferred to the reception room, where a nurse determined their assignment to either the high-dose or low-dose remifentanil group through the sealed envelope method and prepared the remifentanil medication. The high-dose group received 2 mg of 50 mL of NS, and the low-dose group received 0.5 mg of 50 mL of NS. The remifentanil infusion rate (mL/h) was calculated based on the patient's weight and communicated to the anaesthesiologist. The anaesthesiologist, trial data collectors, and patients themselves were blinded to the group assignments.

Anesthetic Procedure

Upon entering the operating room, the patients were monitored by electrocardiogram, oxygen saturation, blood pressure, body temperature, and the bispectral index (BIS, A-2000, Aspect Medical System, USA, software version 3.22, BIS Quattro). Subsequently, 2 mg of midazolam was administered for sedation. Before induction, all patients received an infusion of 10 mL/kg sodium potassium magnesium calcium acetate balance solution (containing 1% glucose) for hydration, and a maintenance fluid rate of 8 mL/kg/h was maintained during the surgery. The induction regimen for both groups consisted of sufentanil at 0.4 μg/kg, propofol targeted-controlled infusion (TCI) at a plasma concentration of 4.5 μg/mL (a TCI of propofol (Diprivan 1% prefilled syringe 10 mg/mL, AstraZeneca UK Limited) was administered using Diprifusor™, software version 2.0, a Graseby 3500 Syringe Pump, Smiths Medical, Watford, UK, while utilizing the Marsh pharmacokinetic model for reference) and rocuronium bromide at 0.2 mg/kg. If the BIS decreased to less than 60 within 3 minutes postinduction, tracheal intubation was performed. After intubation, the plasma propofol concentration was adjusted to 3 μg/mL. The H group and L group were then given continuous infusions of remifentanil at 0.4 μg/kg/

min and 0.1 μg/kg/min, respectively (Yichang Humanwell Pharmaceutical Co., Ltd., batch number 10A02031). The propofol concentration was subsequently adjusted to maintain the BIS between 40 and 60. If the BIS exceeded 60, the propofol TCI concentration was increased by 0.5 μg/mL every 3 minutes to achieve a BIS between 40 and 60; if the BIS fell below 40, the concentration was decreased by 0.5 μg/mL every 5 minutes to reach the target range, ensuring that the propofol plasma concentration never dropped below 1.2 μg/mL. Fifteen minutes before the end of surgery, 30 mg of parecoxib sodium was administered for analgesia, and all skin incisions were infiltrated with 0.5% ropivacaine for pain relief by a gynaecologist before suturing. To prevent postoperative nausea and vomiting, all patients received an intravenous injection of 5 mg dexamethasone combined with 0.075 mg palonosetron after the start of the surgery. Postoperative analgesia was provided to all patients using a patient-controlled analgesia pump with 100 mL of 1 μg/mL sufentanil, no background dose, a bolus of 3 mL, and a lockout time of 10 minutes. Propofol was stopped 5 minutes before the end of surgery, and remifentanil was discontinued at the time of skin closure. The end-tidal carbon dioxide concentration was maintained between 35 and 45 mmHg, with the inspired oxygen concentration set at 50%. All patients were transferred to the postanaesthesia care unit (PACU) for at least 30 minutes of observation after extubation. Hypotension and bradycardia were managed with 8 μg of norepinephrine (if the mean arterial pressure fell below 65 mmHg or if systolic blood pressure in hypertensive patients decreased by more than 30%) and 0.5 mg of atropine (if the heart rate was less than 45 beats/minute), respectively. Hypertension and tachycardia were treated with 10 mg of urapidil (if the systolic blood pressure exceeded 160 or diastolic blood pressure exceeded 100) and 30 mg of esmolol (if the heart rate was more than 100 beats/minute), respectively.

Measurements

OIH is described as a paradoxical increase in sensitivity to painful stimuli following exposure to opioid therapy. The development of OIH may lead to several clinical concerns, including delayed postoperative recovery and hindered timely discharge. Furthermore, it contributes to patient discomfort, elevated pain scores, and increased analgesic consumption. This study evaluated OIH through postoperative pain intensity scores, sufentanil consumption at postoperative various time points after surgery, and the time to the first postoperative analgesic request. Pain intensity was assessed using the Visual Analogue Scale (VAS), with scores ranging from 0 to 10, where 0 indicates no pain. Ten being the worst pain imaginable.

The primary outcomes in this study were the incidence of postoperative nausea and vomiting (PONV), which were recorded before the patients entered the PACU, immediately after PACU admission, and at 30 minutes, 2 hours, 6 hours, 24 hours, and 48 hours after PACU admission.

Secondary Outcomes are as follows: pain scores were assessed immediately upon PACU admission and 30 minutes, 2 hours, 6 hours, 24 hours, and 48 hours after PACU admission using the VAS. The time to first analgesic use within the first 120 minutes postoperatively and the total consumption of sufentanil within 24 and 48 hours postoperatively were also recorded; heart rate and blood pressure were recorded before induction, after induction, after intubation, before incision, after incision, at 30 minutes into the surgery, at 60 minutes into the surgery, at the end of surgery, immediately after extubation, and at 5 minutes after extubation; total consumption of propofol and remifentanil; times to eye-opening, extubation, orientation recovery, and the duration of PACU stay were recorded; the incidences of intraoperative hypotension, hypertension, tachycardia, and bradycardia (definitions provided) and dosages of norepinephrine, atropine, urapidil, and esmolol used were noted.

Statistical Analysis

Continuous variables are presented as the mean (SD) or median (interquartile range) after checking for normality with the Shapiro–Wilk test and were analysed using the unpaired student *t* test or the Mann–Whitney *U*-test, as appropriate. Categorical data are presented as frequencies and percentages and were analysed using the χ^2 test or Fisher's exact test.

The time required for the first postoperative PCA pain rescue in the first 120 postoperative minutes was evaluated by survival analysis (survival was equivalent to "no morphine request"). Kaplan–Meier survival curves were constructed, and the null hypothesis of no difference in survival between groups was tested with the Log rank test. The Cox

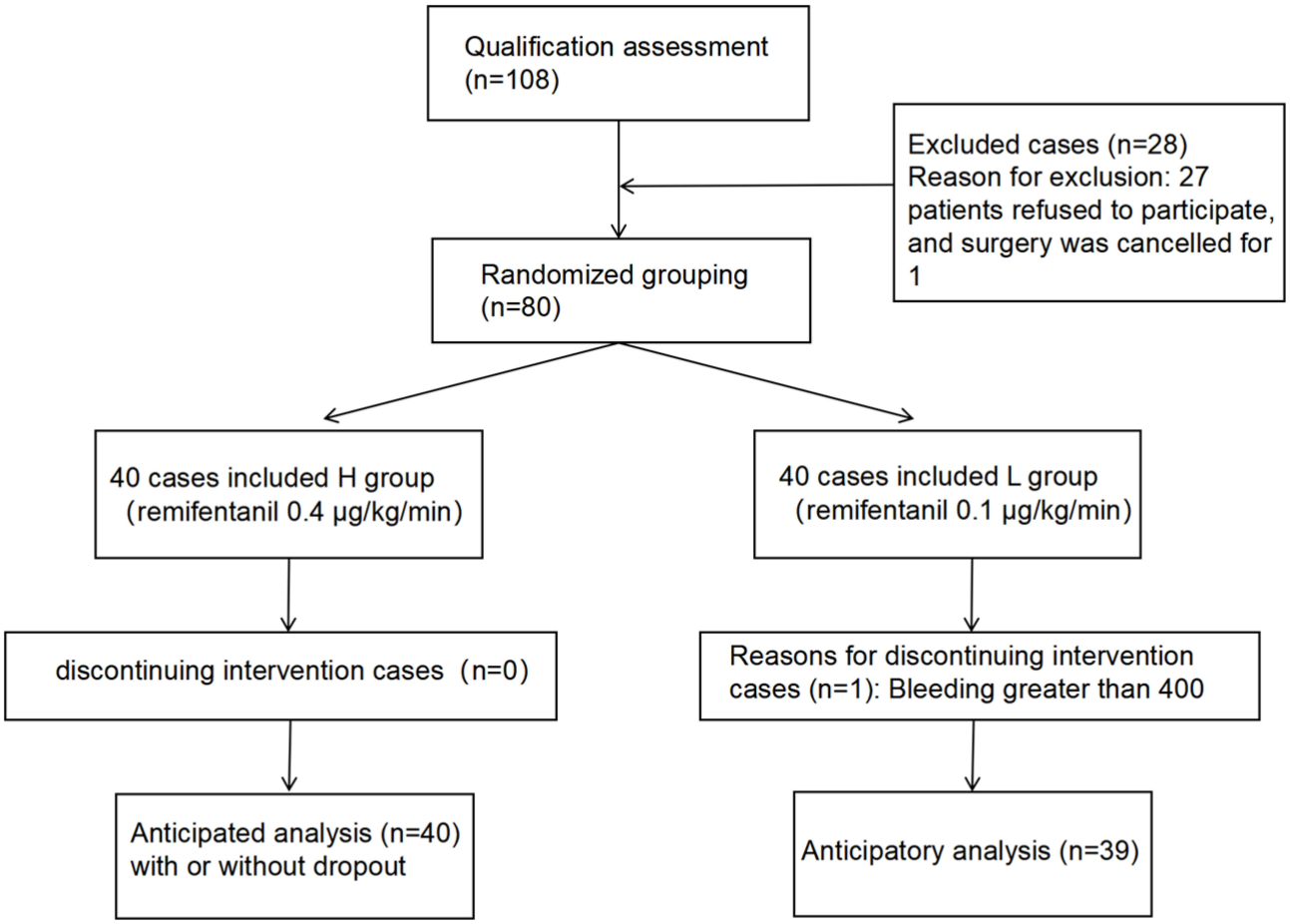

Figure 1 CONSORT flow diagram for the study.

proportional hazards model was employed to calculate the hazard ratio with its relative 95% CI. A P value <0.05 was considered to indicate statistical significance. SPSS Statistics version 15 (SPSS Inc., Chicago, IL, USA).

Results

The recruitment of patients is illustrated in Figure 1. A total of 108 patients were eligible for this study, 27 of whom were excluded due to refusal to participate; in addition, one patient in the low-dose group (L group) withdrew due to intraoperative bleeding greater than 400 mL. Thus, 79 patients were involved in the final analysis. Demographic data show no significant difference between the two groups (all P values > 0.05). (Table 1).

Table 1 Comparison of Demographic Data and Intraoperative Variables Between the High-Dose Remifentanil Group and Low-Dose Remifentanil Group

	H group (N=40)	L group (N=39)	P
Age (Y)	39.23±6.58	41.64±5.51	0.081
Weight (kg)	57.00±6.38	56.83±7.39	0.915
Height (cm)	161.93±16.20	160.03±3.96	0.479
ASA Grading			
I	2540	22/39	0.581
II	15/40	17/39	0.581

(*Continued*)

Table 1 (Continued).

	H group (N=40)	L group (N=39)	P
Hypertension	2/40	3/39	0.953
Anaesthesia duration (min)	117.00±33.73	129.59±33.73	0.139
Operation duration (min)	101.85±35.49	115.21±41.91	0.130
Intraoperative infusion volume (mL)	817.50±270.69	938.46±339.21	0.083
Intraoperative urine output (mL)	147.75±56.25	145.90±25.88	0.954
Dose of propofol (mg)	583.86±235.17	836.27±288.93	0.000*
Remifentanil dose (mg)	2.38±0.81	0.73±0.33	0.000*

Notes: Values are the median ± standard deviation; *P less than 0.05.

The incidences of PONV at 2, 6, 24, and 48 hours postoperatively were 12.5%, 15%, 20% and 20% in high-dose group and 25.6%, 25.6%, 25.6%, and 25.6% in low-dose group. There were no significant differences between group at different time points (all P values > 0.05) (Table 2).

There were no significant differences existed in VAS pain scores at different study time points and sufentanil consumption postoperatively between two groups (Table 3). The time to first PCA request is shown in Figure 2. Analysis using the log-rank (Mantel-Cox) test showed no significant difference between groups (P = 0.1891).

Table 2 Comparison of the Incidence of Nausea and Nausea and Vomiting in Groups H and L at Various Time Points After Surgery

	H group (N=40) n(%)	L group (N=40) n(%)	P
Incidence of nausea and vomiting within 2 hours after surgery	5 (12.5%)	10(25.6%)	0.137
Incidence of nausea and vomiting within 6 hours after surgery	6(15%)	10(25.6%)	0.239
Incidence of nausea and vomiting within 24 hours after surgery	10(20%)	10(25.6%)	0.948
Incidence of nausea and vomiting within 48 hours after surgery	10(20%)	10(25.6%)	0.948
Incidence of vomiting within 2 hours after surgery	2(5%)	3(7.7%)	0.626
Incidence of vomiting within 6 hours after surgery	3(7.5%)	5(10.3%)	0.681
Incidence of vomiting within 24 hours after surgery	4(10%)	6(15.4%)	0.703
Incidence of vomiting within 48 hours after surgery	4(10%)	6(15.4%)	0.703

Table 3 Comparison of VAS Scores at Various Postoperative Time Points and Postoperative Sufentanil Dosages Between Group H and Group L

		H group (N=40)	L group (N=39)	P
VAS grading	Immediately after entering the PACU	1.9 (0.0, 4.1)	1.9 (0.0, 4.1)	0.689
	At 30 min after entering the PACU	3.2 (2.2, 4.9)	3.2 (1.9, 4.1)	0.418
	At 2 hours after entering the PACU	3.2 (1.3, 4.1)	3.2 (1.9, 4.1)	0.765
	At 6 hours after entering the PACU	3.2 (1.1, 4.1)	1.9 (1.1, 4.1)	0.538
	At 24 hours after entering the PACU	0.0 (0.0, 2.8)	1.1 (0.0, 4.1)	0.742
	At 48 hours after entering the PACU	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)	0.691
Sufentanil consumption at 24 hours after surgery (μg)		13.50(6.75, 21)	9(3, 21)	0.262
Sufentanil consumption at 48 hours after surgery (μg)		15(6.75, 24)	9(3, 24)	0.300

Note: Values are medians (quartiles).
Abbreviations: VAS, visual analogue scale.

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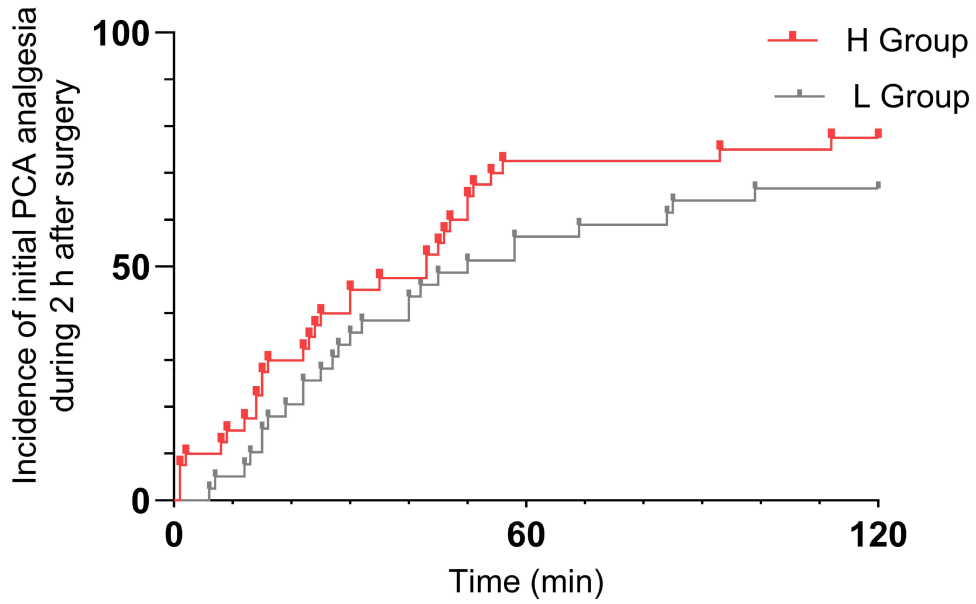

Figure 2 Kaplan-Meier survival curves for the time to the first press of the bolus button for PCA within 2 hours postoperatively for the H group and L group.
Abbreviation: PCA, patient-controlled analgesia.

Propofol consumption was significantly lower in the high-dose group than in the low-dose group (583.86±235.17 mg vs836.27±288.93 mg, P=0.000). The postoperative time to orientation recovery was significantly shorter in the H group than in the L group (6.5±4.8 versus 8.7±4.4; P = 0.036) (Table 4). The variation of MAP and HR at different study time points are shown in Figure 3.

Side effects are summarized in Table 5. The incidence of hypotension and consumption of norepinephrine was significant higher in H group than in the L group, P = 0.022 and 0.005, respectively.

Discussion

The main finding of this study showed that using a high dose of remifentanil was not associated with an increasing incidence of PONV, when comparing with a low dose. There was no significant difference in postoperative vas as well as postoperative sufentanil consumption. A significant difference in propofol consumption and incidence of hypotension were found between using high and low dose of remifentanil.

The incidence of PONV associated with remifentanil dosage in total general anesthesia still remains controversial. A retrospective analysis conducted by Jun Hozumi et al reported that a remifentanil dose greater than 0.2 μg/kg/min was a risk factor for PONV.[5] Conversely, two meta-analyses involving mostly patients under inhalational anaesthesia showed that higher doses of remifentanil did not increase PONV.[13,14] In the present study, despite a fourfold disparity in perioperative remifentanil dosage between the groups, no statistically significant difference was observed in the incidence

Table 4 Comparison of Orientation Recovery Time, Extubation Time and PACU Stay Time Between Group H and Group L

	H group (N=40)	L group (N=39)	P
Orientation recovery time (min)	6.5±4.8	8.7±4.4	0.036*
Postoperative extubation time (min)	6.3±4.9	6.9±4.8	0.617
Residence time in the PACU (min)	31.9±3.3	31.8±3.9	0.922

Notes: *P less than 0.05.

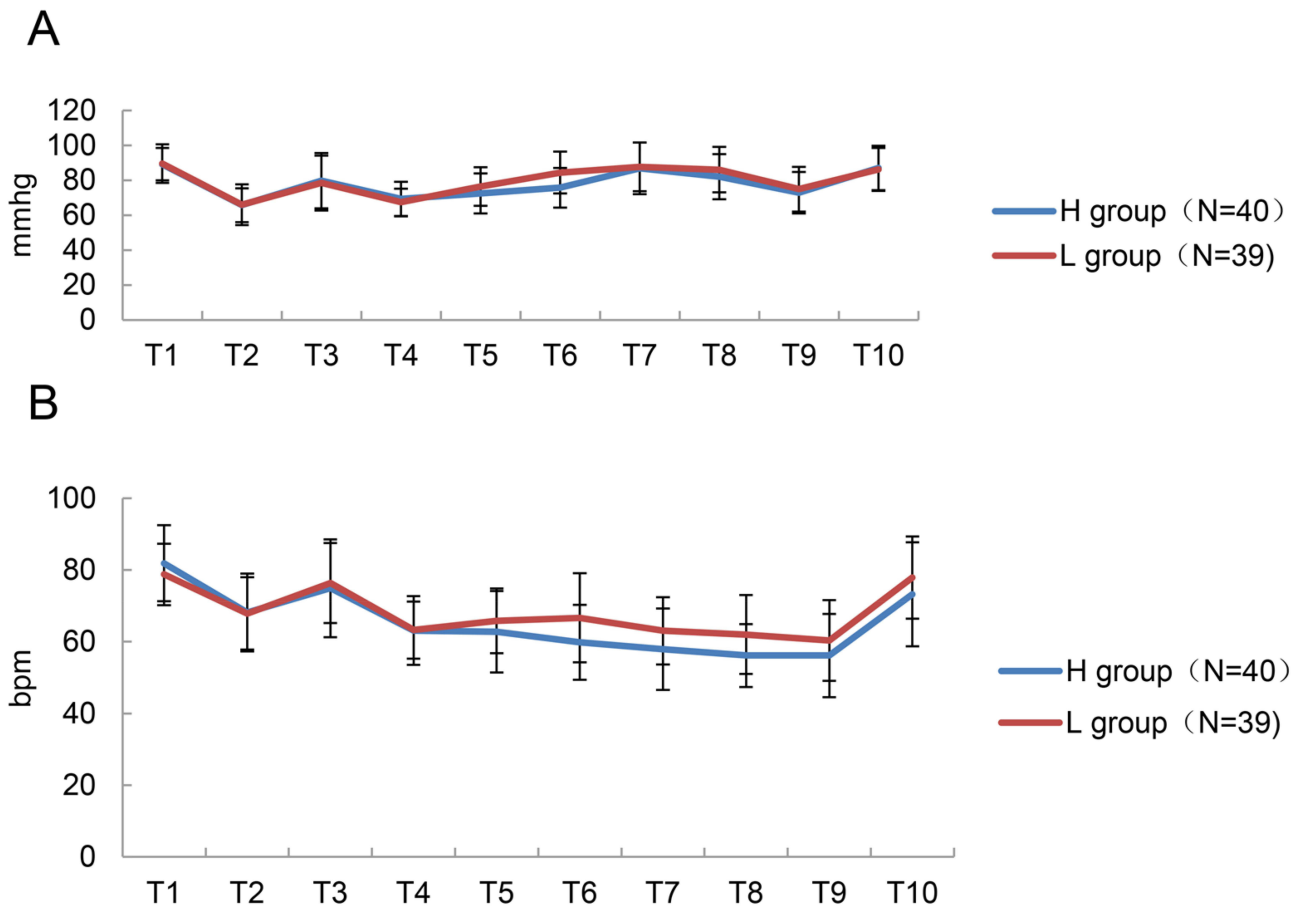

Figure 3 (**A**) Comparison of perioperative mean arterial pressure between the two groups. (**B**) Comparison of perioperative heart rate between the two groups. Group (H) High-dose remifentanil group. Group (L) Low-dose remifentanil group. T1, before induction. T2, before intubation. T3, after intubation. T4, before skin incision. T5, after skin incision. T6, at 5 min after skin incision. T7, at 30 min after skin incision. T8, at 60 min after skin incision. T9, completion of the operation. T10, immediately after extubation.

of PONV when comparing high-dose and low-dose administration of this class of opioids. Our findings suggest that the clinical utilization of remifentanil should be guided by the necessity for effective pain management, warranting the administration of higher doses without compromising an elevated risk of PONV. The following factors may contribute to our findings: First, the protocol for induction and maintenance of anesthesia in this study was based on propofol TIVA,

Table 5 Comparison of the Intraoperative Incidence Rates of Adverse Events Associated with Vasoactive Drug Intervention Between Group H and Group L

	H group (N=40)	L group (N=39)	P
Incidence of intraoperative hypertension n (%)	5 (12.5%)	8(20.5%)	0.337
Incidence of intraoperative hypotension n (%)	15(37.5%)	6 (15.3%)	0.022*
Incidence of intraoperative tachycardia n (%)	0(0%)	0(0%)	–
Incidence of intraoperative bradycardia n (%)	11(27.5%)	4(10.3%)	0.051
Intraoperative norepinephrine dosage (ug)	0(0, 8)	0(0, 0)	0.005*

Notes: Values are the mean ± standard deviation or n/N (%), intraoperative norepinephrine dosage (ug) Values are medians (quartiles). *P less than 0.05.

Abbreviations: PONV, postoperative nausea and vomiting; TIVA, Total Intravenous Anesthesia; BIS, Bispectral Index; VAS, Visual Analogue Scale; PCA, Patient Controlled Analgesia; PACU, Post Anesthesia Care Unit; ASA, American Society of Anesthesiologist; NS, Normal Saline; TCI, Target Controlled Infusion; WHO, World Health Organization; SD, Standard Deviation; MAP, Mean Arterial Pressure; OIH, Opioid-Induced Hyperalgesia; NMDA, N-Methyl-D-Aspartate; MOR, Mu-Opioid receptor.

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which effectively reduces the incidence of PONV compared to inhalational anaesthetics, which was approved by Ma et al[15] study. Second, it is possible that its pharmacological characteristics result in a higher affinity for MOR1 rather than MOR2, while the emetic effects primarily mediated by MOR2.[16]

Our study also found no significant differences in VAS scores at various postoperative time points, sufentanil rescue doses, or time to first postoperative sufentanil request between the two groups. Two comparable studies investigating high-dose remifentanil (target-controlled concentrations of 8ng/mL or 1.2μg/kg/min) versus low-dose regimens (4ng/mL or 0.2μg/kg/min) in endoscopic nasal and thyroid surgeries reported similar outcomes, showing no significant intergroup differences in mechanical pain thresholds or VAS scores, with some instances of lower VAS scores in high-dose groups.[17,18] These investigations share notable methodological consistencies: 1) inclusion of minimally invasive procedures with limited nociceptive stimulation and 2) exclusive use of propofol-remifentanil TIVA without volatile anesthetics. Notably, SU et al[19] observed significantly lower postoperative VAS scores with high-dose remifentanil combined with propofol TIVA compared to sevoflurane-based anesthesia, suggesting that propofol-based TIVA might mitigate remifentanil-induced hyperalgesia. Intriguingly, experimental evidence indicates that prolonged high-dose remifentanil infusion (18ng/mL for 1h) may paradoxically reverse established hyperalgesia in herpes zoster patients, while preclinical studies demonstrate its protective effects against spinal transection-induced hyperalgesia.[20,21] At minimum, our clinical data provide no evidence of enhanced hyperalgesia or compromised postoperative recovery associated with high-dose remifentanil administration in gynecological laparoscopic surgeries.

The velocity and quality of patient emergence from general anesthesia represent significant concerns for clinical anesthesiologists. It is interesting that the time to recovery of orientation was approximately 2 minutes faster in the high-dose remifentanil group than in the low-dose remifentanil group, although this difference did not reach clinical significance. We speculated that this may be due to the decreased consumption of propofol (836.27 ± 288.93 mg vs 583.86 ± 235.17 mg). Our findings demonstrate a negative correlation between the dose of remifentanil and propofol when guided by BIS monitoring to maintain the depth of anesthesia. Therefore, further investigations are warranted to ascertain the optimal compatibility of these two medications while considering their respective advantages and disadvantages.

In this study, we acknowledge that there are some limitations. First, as a pilot study, we recruited 80 patients in an expedited manner to participate, which would inevitably result in a reduced statistical power to discern any differences in the primary outcome between the two groups. Further large sample size studies are warranted. Second, regarding the potential for high-dose remifentanil to cause pain sensitization, we did not employ classical thermal and mechanical noxious stimulation tests[22] but only compared postoperative first analgesic demand timing, VAS scores, and remedial doses. Strictly speaking, our study offers no conclusions on allodynia or hyperalgesia,[23] but from the perspective of acute pain management, high-dose remifentanil does not increase postoperative pain.

Conclusion

Our study indicates that high-dose remifentanil TIVA does not increase the incidence of postoperative PONV or pain sensitization, substantially decreases the propofol requirement, and facilitates rapid patient recovery.

Data Sharing Statement

The datasets and materials used during the current study are available from the corresponding author on reasonable request.

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Ethics Approval and Consent to Participate

The clinical trials study was reviewed and approved by Ethics Committee of Zhejiang provincial Hospital of Chinese medicine and the participants were recruited after written informed consent was obtained.

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Disclosure

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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