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Effects of Estazolam, Remimazolam and their Combination on Preoperative Anxiety and Postoperative Pain a ter Gynecological Laparoscopic Surgery: A Double-Blind, Randomized, Controlled Trial

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Abstract

Purpose: Preoperative anxiety is closely related to postoperative pain, and high pre-operative anxiety can aggravate postoperative pain. We aimed to estimate the effect of estazolam, remimazolam, and their combination on preoperative anxiety and postop-erative pain in patients undergoing elective gynecological laparoscopic surgery.

Materials and methods: We carried out a randomized, double blind, placebo controlled experiment between October 2020 and April 2021. A total of 108 patients were split into four groups: (1 mg estazolam or starch was taken orally on the evening before surgery; 0.1 mg/kg remimazolam or normal saline was administered intravenously after entering the operating room) group E received estazolam and normal saline; group R received starch and remimazolam; participants in group ER were given not only estazolam but also remimazolam; participants in group C were given starch and normal saline. We recorded preoperative anxiety scores (Visual Analog Scale-Anxiety (VAS-A)), pain scores (VAS), and cumulative sufentanil consumption after laparoscopic surgery.

Results: The mean anxiety scores were significantly lower in group E, R, and ER than in group C before surgery. Compared with group C, mean pain scores were significantly lower in Group ER at 0.5, 1, 4, 8, 24, 48, and 72 hours after surgery and lower in group R or E, at 4, 8, and 24 hours after surgery. The mean pain scores in group E (at 8 and 24 postoperative hours) and group R (at 8 postoperative hours) were both significantly higher than those in group ER. Moreover, the mean cumulative sufentanil consumption was significantly lower in Group ER at 0.5, 1, 4, 8, 24, 48, and 72 hours after surgery and lower in group E or R at 0.5 hours after surgery, com-pared with group C.

Conclusion: The preoperative application of estazolam, remimazolam, and their combination can relieve preoperative anxiety and postoperative pain for patients undergoing gynecological laparoscopic surgery. Moreover, the preoperative combination can also significantly reduce postoperative sufentanil consumption.

Keywords: Anxiety; Remimazolam; VAS; Constipation; BMI; PCA

Introduction

Although surgical methods and surgeons' operating techniques are constantly improving, most patients still experience at least moderate pain after laparoscopic surgery [1-3]. Postoperative pain leads to increased demand for opioids, which are associated with several side effects, such as pruritus, sedation, respiratory depression, and constipation. Perception of postoperative pain is complex and is associated with both physical and psychological factors. One important factor is the level of preoperative anxiety; patients who are more anxious have been reported to have a significantly higher likelihood of experiencing postoperative pain [4,5]. Furthermore, female patients are more prone to be anxious before surgery [6]. Therefore, patients undergoing gynecological laparoscopic surgery were selected as study participants to explore whether the preoperative application of benzodiazepines could reduce preoperative anxiety and, subsequently, relieve postoperative pain.

Benzodiazepines are the most widely used anxiolytic drugs in preoperative preparation. Numerous clinical trials have investigated the effects of benzodiazepines on preoperative anxiety and postoperative pain, but these studies have yielded inconsistent conclusions. In a randomized controlled trial, oral midazolam did not relieve postoperative pain, although it reduced preprocedural anxiety when compared with the control group [7]. We suppose that these results could be related to the weak anxiolytic effect of a single medication or the slow onset of oral medication.

Considering that most patients feel anxious during the night before surgery, we planned an early anxiolytic intervention on the evening before surgery. Estazolam was an appealing option

because it has been used safely at bedtime with good anxiolytic and hypnotic effects. Remimazolam is a new type of ultra-short acting benzodiazepine indicated for rapid preoperative anti-anxiety before surgery due to fast onset, rapid metabolism, and short recovery time.

To date, few clinical studies have investigated these two drugs. In this trial, three different anxiolytic regimens-oral estazolam alone, intravenous remimazolam alone, or a combination of both were administered and compared in terms of their effects on preoperative anxiety and postoperative pain among gynecological patients prior to laparoscopic surgery.

Materials and Methods

Study sample

Patients were enrolled in this study if they were scheduled to undergo gynecological laparoscopic surgery and rated as American Society of Anesthesiologists (ASA) class I or II between October 2020 and April 2021. Additionally, patients were required to meet the following conditions: Between the ages of 18 and 65 years, with a Body Mass Index (BMI) of 18-30 kg/m^2, and diagnosed with non-malignant conditions. During the pre-anesthesia interview, all participants received full explanations of the study procedures, trial regimens, and how to use Patient Controlled Analgesia (PCA) devices. All participants provided written informed consent before participating.

Patients were excluded if they had taken oral (sedative) analgesics (for example, ben-zodiazepines, barbiturates, non-steroidal anti-inflammatory drugs, opioid analgesics) within 14 days before surgery. Individuals with a history of mental illness, alcohol abuse, drug abuse, or chronic pain were also excluded, as well as patients with known contraindications or allergies associated with the use of benzodiazepines, patients with cardiopulmonary dysfunction or severe liver and kidney dysfunction, patients unable to understand the meaning of the scoring scales or unable to master the use of self-control analgesia pumps.

Patients who changed surgical methods (laparoscopic surgery converted to open surgery) and those who were diagnosed with malignant tumors intraoperatively were excluded. We also excluded patients whose intraoperative blood loss exceeded 800 mL (or blood loss per hour >200 mL), whose operations lasted longer than 2 hours, as well as those whose postoperative follow-up data were lost or unavailable.

Study design

This was a prospective, placebo-controlled, and double blind study in which patients were randomly enrolled into four groups using envelopes with codes generated using a random number table. To maintain blinding, investigators, clinicians, and patients were all fully unaware of treatment allocation. The drug solutions were prepared by an anesthesiologist who was not involved in the management of the patients. The Medical Ethics Committee of First People's Hospital of Lianyungang approved this study (ethics: KY-20200627001-02) on 24 July 2020, and it is registered in the Chinese Clinical Trial Registry (ChiCTR2000037489) on 28 August 2020. The study protocol followed the CONSORT guidelines. The sample size was calculated based on the primary outcome of VAS scores of pain intensity. This study was based on an effect size of 0.37, according to the pre-experiment data of resting pain scores half an hour after surgery, an alpha error of 0.05, statistical power of 0.85, and an expected dropout rate of 10% for each group. Therefore, we ultimately intended to recruit a total of 108 subjects (GPower 3.1.9.2, USA).

Drug prescription method

Patients in group E (n=27) received a capsule containing estazolam (1 mg) at 8:00 p.m. on the evening before surgery and an intravenous injection of normal saline (0.1 mL/kg) after entering the operating room. Patients in group R (n=27) received a capsule containing starch (1 mg) at 8:00 p.m. on the evening before surgery and an intra-venous injection of remimazolam (0.1 mg/kg) after entering the operating room. Remimazolam solution was formulated to 1 mg/mL. Patients in group ER (n=27) were not only given estazolam (1 mg) orally at 8:00 p.m. on the evening before surgery but were also injected with remimazolam (0.1 mg/kg) intravenously after entering the operating room. Patients in the placebo group (group C, n=27) were given a capsule containing starch (1 mg) on the evening before surgery and normal saline (0.1 mL/kg) after entering the operating room. No other preoperative medications were administered before the induction of anesthesia.

Anesthesia management was consistent in all patients. General anesthesia induction drugs consisted of cisatracurium (0.2 mg/kg), propofol (2 mg/kg), and sufentanil (0.3 μg/kg). Additionally, the patients received intravenous propofol, combined with remifentanil, as needed to maintain general anesthesia. The anesthesiologist added cisatracurium intravenously, as necessary, during the operation. The goal was to keep the bispectral index at 40-60 and the heart rate at 50-110 bpm until the end of anesthesia. The range of intraoperative mean arterial blood pressure was limited to 20% of the preoperative baseline values. After patients were extubated and resumed spontaneous respiration after surgery, they were transferred to the post-anesthesia care unit for close monitoring, including of vital signs.

All patients received a sufentanil PCA pump with the same postoperative analgesic dose based on the patient's weight (2 μg/kg) and diluted to 100 mL with normal saline (continuous infusion rate 2 mL/h). Additional analgesia requirements could be met by pressing the automatic analgesia pump button (single dose 0.04 μg/kg) with a lockout period of 15 minutes. Finally, the consumption of sufentanil could be viewed on a computer monitor. If Postoperative Nausea and Vomiting (PONV) occurred, the patient would be given 5 mg of intravenous tropisetron.

Outcome assessment

The primary outcome measures were (1) The VAS scores of pain intensity during rest and movement, measured at 0.5, 1, 4,

8, 24, 48, and 72 postoperative hours (0=no pain; 10=worst imaginable pain); and (2) The cumulative sufentanil consumption at 0.5, 1, 4, 8, 24, 48, and 72 postoperatively hours. The secondary outcomes were (1) The preoperative anxiety scores assessed using a 10-point VAS during the preoperative visit, after entering the operating room, and 10 minutes after remimazolam or normal saline administration (0=no anxiety; 10=worst imaginable anxiety); (2) The Ramsay sedation scale score at 30 postoperative minutes; (3) Operation duration and intraoperative medication; (4) Extubation time; (5) PONV; (6) Length of stay in the hospital; and (7) The Numerical Rating Scale (NRS) score of patient satisfaction with regard to anesthesia (0=very dissatisfied; 10=very satisfied).

Statistical analysis

SPSS Statistics for Windows, version 26.0 for (IBM Corp., Armonk, NY, USA) was used to analyze data. $P<0.05$ was considered statistically significant. Mean ± standard deviation is used to present data with normal distributions, which were compared by one-way ANOVA test or two-way repeat measured ANOVA as appropriate. Otherwise, data are presented as medians with confidence intervals, and the non-parametric Kruskal-Wallis test or generalized estimating equation was used for comparison. The enumeration data was measured using the chi-square test or Fishers exact test. Spearman rank correlation was used to test the correlation among anxiety measures.

Results

Demographic and baseline characteristics

The participant inclusion and exclusion flow chart is presented in **Figure 1**. There were 100 participants enrolled from 120 women screened for study eligibility between October 2020 and April 2021. About 25 women were recruited for each group. The reasons for study exclusion were failure to meet inclusion criteria or declining to participate. Additionally, eight patients discontinued the study for the following reasons: intraoperative transition to open surgery, intraoperative massive blood loss >800 mL, intraoperative diagnosis of malignant tumor, and operation time >2 hours. Demo-graphic characteristics are presented in **Table 1**. There were no statistically significant differences between the groups with regard to age, ASA class, weight, BMI, previous surgery, or type of elective surgery.

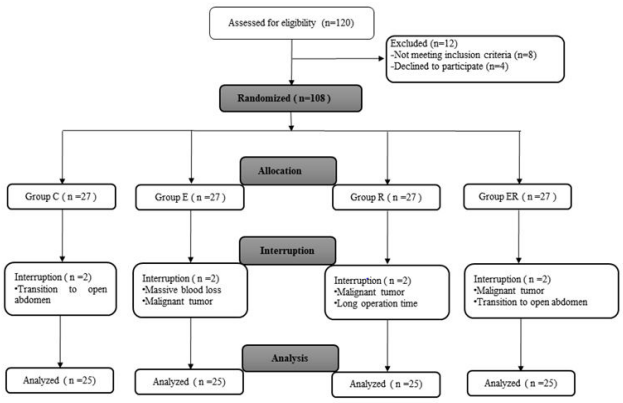

Figure 1: Study flow chart.

Table 1: Demographical and clinical variables.

	Group C (n=25)	Group E (n=25)	Group R (n=25)	Group ER (n=25)
Patient age (years)	45.44 ± 8.00	47.16 ± 6.40	46.60 ± 9.33	47.84 ± 7.40
ASA, I/II (n)	21/4	20/5	19/6	21/4
Weight (kg)	65.08 ± 7.81	64.28 ± 9.70	61.44 ± 6.10	61.84 ± 7.59
BMI (kg/m^2)	24.90 ± 2.39	24.90 ± 2.89	24.35 ± 2.82	23.91 ± 2.14
Previous surgery (n)	12	10	12	13
Type of elective surgery				
Laparoscopic total hysterectomy (n)	16	12	13	15
Laparoscopic myomectomy (n)	9	13	12	10

Note: Data are presented as mean ± standard deviation or n (%) unless otherwise specified. BMI: Body Mass Index.

Primary outcomes

Compared with group C, mean pain scores (VAS) were significantly lower in group ER at 0.5, 1, 4, 8, 24, 48, and 72 hours after surgery and lower in group E or group R at 4, 8, and 24 hours after surgery. Compared with group ER, the mean pain scores in group R at 8 hours after surgery and in group E at 8 and 24 hours after surgery were both significantly higher (**Table 2**).

Moreover, the cumulative sufentanil consumption was significantly lower in group ER at 0.5, 1, 4, 8, 24, 48, and 72 hours after surgery and lower in group E or R at 0.5 hours after surgery, compared with group C. Compared with group E and group R, the cumulative sufentanil consumption in group ER was significantly lower at 4, 8, and 24 hours after surgery (**Table 3**).

Table 2: Postoperative pain score.

	Group C (n=25)	Group E (n=25)	Group R (n=25)	Group ER (n=25)
VAS-R, 0.5 h	2.46 ± 0.63	2.10 ± 0.86	2.20 ± 0.85	1.78 ± 0.81[a]
VAS-M, 0.5 h	3.50 ± 0.69	3.13 ± 0.87	3.30 ± 0.69	2.93 ± 0.63[a]
VAS-R, 1 h	2.76 ± 0.88	2.33 ± 0.82	2.42 ± 0.78	2.01 ± 0.75[a]
VAS-M, 1 h	3.81 ± 0.87	3.37 ± 0.71	3.36 ± 0.84	3.00 ± 0.87[a]
VAS-R, 4 h	2.91 ± 0.87	2.24 ± 0.91[a]	2.37 ± 0.79[a]	1.92 ± 0.87[a]
VAS-M, 4 h	3.64 ± 0.88	2.95 ± 0.87[a]	3.12 ± 0.89[a]	2.67 ± 0.87[a]
VAS-R, 8 h	2.56 ± 0.75	2.01 ± 0.88[a]	1.92 ± 0.76[a]	1.40 ± 0.73[abc]
VAS-M, 8 h	3.72 ± 0.85	2.82 ± 0.87[a]	2.84 ± 0.61[a]	2.48 ± 0.80[a]
VAS-R, 24 h	2.63 ± 0.82	1.80 ± 0.85[a]	1.74 ± 0.84[a]	1.42 ± 0.81[a]
VAS-M, 24 h	3.50 ± 0.79	2.87 ± 0.79[a]	2.67 ± 0.86[a]	2.33 ± 0.88[ac]
VAS-R, 48 h	1.41 ± 0.62	1.06 ± 0.56	1.26 ± 0.76	0.94 ± 0.58[a]
VAS-M, 48 h	2.54 ± 0.73	2.26 ± 0.83	2.18 ± 0.66	1.97 ± 0.65[a]
VAS-R, 72 h	0.69 ± 0.45	0.58 ± 0.42	0.52 ± 0.31	0.39 ± 0.29[a]
VAS-M, 72 h	1.75 ± 0.75	1.53 ± 0.64	1.37 ± 0.84	1.20 ± 0.56[a]

Note: Data are presented as mean ± standard deviation.

VAS-R: VAS score during Rest; VAS-M: VAS score during Movement.

[a]Statistically significant (P<0.05) difference versus group C, [b]versus group R, and [c]versus group E.

Table 3: Postoperative sufentanil consumption (μg).

	Group C (n=25)	Group E (n=25)	Group R (n=25)	Group ER (n=25)
Sufentanil, 0.5 h	3.60 (1.25~4.05)	1.40 (1.20~3.27)[a]	1.20 (1.15~1.45)[a]	1.26 (1.14~1.38)[a]
Sufentanil, 1 h	5.20 (2.66~8.42)	4.40 (2.66~5.80)	4.46 (2.40~5.97)	2.60 (2.40~3.54)[a]
Sufentanil, 4 h	13.00 (10.94~15.60)	13.40 (11.04~16.80)	13.00 (9.60~16.80)	10.40 (9.03~12.00)[abc]
Sufentanil, 8 h	23.40 (21.83~27.80)	23.04 (19.86~29.00)	24.00 (20.89~29.14)	20.80 (17.28~22.36)[abc]
Sufentanil, 24 h	50.32 (43.65~57.60)	47.88 (38.92~66.06)	43.20 (27.60~63.03)	36.72 (24.00~52.66)[a]

Sufentanil, 48 h	52.00 (45.60~73.44)	49.00 (40.18~86.65)	43.20 (27.60~65.71)	37.12 (24.00~59.22)[a]
Sufentanil, 72 h	52.00 (45.60~73.44)	49.00 (40.18~86.65)	43.20 (27.60~65.71)	37.12 (24.00~59.72)[a]

Note: Data are presented as median (IQR).

[a]Statistically significant (P<0.05) difference versus group C, [b]versus group R, and [c]versus group E.

Secondary outcomes

The mean preoperative anxiety scores determined after patients entered the operating room for patients taking estazolam orally before bedtime (group E and group ER) were significantly lower than those for patients who did not receive estazolam during the night before surgery (group C and group R). The mean anxiety scores determined 10 minutes after preoperative administration were significantly lower among patients who were given remimazolam (group R and group RE) than among those who were not (group C and group E). Additionally, compared with group C, the mean anxiety score of group E was significantly lower 10 minutes after saline treatment (**Table 4**).

Table 4: Preoperative anxiety score.

	Group C (n=25)	**Group E (n=25)**	**Group R (n=25)**	**Group ER (n=25)**
VAS-A, TI	4.79 ± 0.67	4.89 ± 0.73	5.02 ± 0.74	4.76 ± 0.71
VAS-A, T2	6.63 ± 0.86	4.92 ± 0.87[ab]	6.72 ± 0.87	4.68 ± 0.83[ab]
VAS-A, T3	5.39 ± 0.97	4.91 ± 0.54[a]	3.23 ± 0.58[ac]	2.92 ± 0.82[ac]

Note: Data are presented as mean ± standard deviation.

TI: During the preoperative visit; T2: After going into the operating room; T3: 10 minutes after giving remimazolam or NS.

[a]Statistically significant (P<0.05) difference versus group C, [b]versus group R, and [c]versus group E.

Table 5 lists other intraoperative and postoperative data. There were no statistically significant intergroup differences in mean Ramsay sedation scale scores at 30 post-operative minutes, intraoperative propofol and remifentanil consumption, duration of surgery, incidence of PONV, or length of stay in hospital. Finally, satisfaction rates with regard to anesthesia in group E, group R, and group ER were significantly higher than that of group C.

Table 5: Intraoperative and postoperative data.

	Group C (n=25)	**Group E (n=25)**	**Group R (n=25)**	**Group ER (n=25)**
Ramsay sedation scale, 0.5 h	2.00 ± 0.00	2.00 ± 0.00	2.00 ± 0.00	2.00 ± 0.00
Remimazolam consumption (mg)	0.00 ± 0.00	0.00 ± 0.00	6.14 ± 0.61	6.18 ± 0.76
Intraoperative propofol consumption (mg)	562.20 ± 163.37	553.44 ± 159.09	551.64 ± 172.42	543.16 ± 163.07
Intraoperative remifentanil consumption (μg)	898.20 ± 243.00	795.04 ± 242.89	839.36 ± 252.38	780.76 ± 188.67
Length of surgery (min)	97.68 ± 17.07	95.08 ± 17.55	92.00 ± 15.86	96.52 ± 15.82

Nausea-vomiting, no. (%)	10 (40)	9 (36)	8 (32)	8 (32)
Length of stay (d)	5.60 ± 1.47	6.16 ± 1.49	5.76 ± 1.62	5.44 ± 1.26
Satisfaction score	8 (7.5~9)	9 (8~10)[a]	9 (8.5~10)[a]	10 (9~10)[a]

Note: Data are presented as mean ± standard deviation or n (%) unless otherwise specified.

[a] Statistically significant (P<0.05) difference versus Group C.

Discussion

We investigated whether the administration of 1 mg oral estazolam, 0.1 mg/kg intra-venous remimazolam, or a combination of these would be beneficial for reducing preoperative anxiety and postoperative pain in gynecological patients undergoing laparoscopic surgery.

Currently, laparoscopic surgery is widely chosen by gynecologists and patients due to the associated minimal invasiveness and surgical trauma, as well as fast recovery [8,9]. However, postoperative pain caused by laparoscopic surgery is still inevitable. It is generally accepted that approximately 5% to 30% of patients undergoing abdominal hysterectomy experience severe postoperative pain [10] which can lead to opioid abuse after surgery. Although opioids have superior analgesic effects, they are not considered ideal by some surgeons due to side effects, such as PONV, respiratory depression, and intestinal obstruction [11].

Various approaches to relieving postoperative pain and reducing opioid consumption have been studied in patients undergoing various operations. The present study aimed to investigate whether postoperative pain could be alleviated by reducing preoperative anxiety. Preoperative anxiety is a preoperative psychological reaction, mainly caused by worry and fear about surgery [12]. Additionally, female gender is an independent risk factor for preoperative anxiety [6] and female patients have been reported to have lower pain thresholds and to experience greater pain intensity than males [13,14]. Therefore, this study selected female patients undergoing elective gynecological surgery as participants. Preoperative anxiety is closely associated with perioperative anesthesia and postsurgical management factors, including postoperative pain, anesthetic requirements, hemodynamic abnormalities, and wound healing [15].

Several studies have reported that perioperative anxiety can lead to postoperative hyperalgesia. It has been observed that preoperative anxiety levels can significantly affect postoperative pain, particularly in obstetric and gynecological surgery [16,17]. This may be related to the fact that female patients are more likely to have anxiety before surgery. Clinically, it has been reported that anti-epileptic drugs and anti-anxiety drugs can combat preoperative anxiety and relieve postoperative pain. Shimony, et al., [18] concluded that perioperative use of pregabalin could attenuate preoperative anxiety, as well as reduce postoperative pain scores and analgesic usage without increasing the incidence of adverse events. Similarly, preoperative oral gabapentin was effective for reducing not only preoperative anxiety but also postoperative pain and morphine consumption in morbidly obese patients who had undergone laparoscopic sleeve gastrectomy [19]. Moreover, other studies have suggested that adults undergoing outpatient dermatologic surgery, dental surgery, and endoscopic procedures benefit from oral midazolam because it is safe and effective for reducing perioperative pain, anxiety, or both [20,21]. However, Bayer, et al., [7] found out that although 10 mg of oral midazolam reduced preprocedural anxiety, it did not reduce pain associated with uterine aspiration during first trimester surgical abortions. Their experimental design was similar to ours but with somewhat different results, which may be related to the mode and timing of administration.

The mechanism by which preoperative anxiety causes postoperative pain aggravation is still unclear. Wu, et al., [22,23] revealed that preoperative anxiety could cause hyperalgesia by means of impairing the GABAergic system. In our study, we selected two GABAA receptor agonists-intermediate-acting estazolam and ultra-short-acting remimazolam. Estazolam is a sedative, hypnotic, and anxiolytic drug, which is often used before bed by patients with anxiety. Remimazolam is a novel benzodiazepine with quick onset, short maintenance, short recovery time, no accumulation of metabolism, and no serious side effects, which is suitable for quickly relieving tension for patients before surgery. Remimazolam is now mostly used as an anticonvulsant and an intensive care tranquilizer. More clinical trials are needed to determine whether the application of estazolam and remimazolam in combination or separately can reduce preoperative anxiety and postoperative pain by acting on GABAA receptors. The drug dosage selection in this study was based on preliminary experimental results. We found that the mean preoperative anxiety scores determined after patients entered the operating room of patients who took oral estazolam before bedtime were significantly lower than those of patients who did not take bedtime estazolam. The mean anxiety scores measured 10 minutes after preoperative administration were significantly lower among patients who were given remimazolam than among those who were not. The mean pain scores (VAS) were significantly lower in the combination group at 0.5, 1, 4, 8, 24, 48, and 72 hours after surgery and lower in the estazolam or remimazolam groups at 4, 8, and 24 hours after surgery, compared with the placebo group. The mean cumulative sufentanil consumption was significantly lower in the combination group at 0.5, 1, 4, 8, 24, 48, and 72 hours after surgery and lower in the estazolam or remimazolam group at 0.5 hours after surgery, compared with the placebo group. There

was no excessive sedation in the preoperative administration groups. Additionally, anesthesia satisfaction was significantly higher among patients who received estazolam or remimazolam preoperatively.

An important limitation of the study was that it did not take into account patients undergoing emergency gynecological surgery. Also, we only took female (gynecology) patients into consideration. Finally, we only used benzodiazepines in the study. Future studies should extend the inclusion criteria, and the most suitable drug dosage for reducing preoperative anxiety to relieve postoperative pain should be studied thoroughly. Moreover, the effects of other anxiolytic drugs on postsurgical pain should be researched.

Conclusion

In conclusion, preoperative administration of estazolam, remimazolam, and their combination is beneficial in terms of reductions in preoperative anxiety and postoperative pain without excessive sedation for patients undergoing gynecological laparoscopic surgery. Moreover, the preoperative combination can reduce postoperative sufentanil consumption, which further optimizes the clinical effects.

Data Availability Statement

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

Authors' Contributions

Study design: Ji-Ying Feng, Nan Chen;

Patient recruitment: Yun Wang, Xue Zhang, Nan Chen;

Randomization and allocation: Rui-Jia Gao, Yu Huang;

Data acquisition and analysis: Ying Wang, Yun Wang, Xin-Dan Zhang;

Drafting the manuscript: Ying Wang, Xue Zhang, Xin-Yue Chen, Nan Chen;

Revision of the manuscript: all authors. All authors read and approved the final manuscript.

Funding Statement

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Conflicts of Interest Statement

No competing financial interests exist.

Ethics Approval Statement

The medical ethics committee of first people's hospital of Lianyungang had approved this study.

Patient Consent Statement

Informed consent has been obtained from all participants.

Clinical Trial Registration

Chinese Clinical Trial Registry (ChiCTR2000037489).

Consent for Publication

Not applicable.

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