The Second Xiangya Hospital of Central South University

(Investigator-initiated) Clinical Research Protocol

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Project Title: Series Study on the Application of G Protein-Biased Receptor Agonist Oliceridine in Gynecological Surgery Based on ERAS Principles (2): Effects of Oliceridine Versus Sufentanil on Postoperative Nausea and Vomiting After Gynecological Laparoscopic Surgery

Sponsor: None

Initiating Institution: The Second Xiangya Hospital of Central South University

Leading Unit Information: Single-center

Research Nature/Type: Interventional/Randomized Controlled Clinical Trial

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Application Specialty: Anesthesiology

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1. Research Background and Rationale

Postoperative nausea and vomiting (PONV) is a common complication following surgery. Reports indicate that the incidence of PONV is 30% among all postoperative patients and can reach up to 80% in high-risk patients. Well-established risk factors for increased PONV include female sex, age under 50 years, non-smoking status, and a history of PONV or motion sickness [1, 2]. PONV not only diminishes patients' well-being, but may also result in severe consequences such as dehydration, electrolyte imbalance, wound dehiscence, and regurgitation with aspiration. These complications can lead to delayed recovery, unplanned hospital admission, and postponed return to work. Such outcomes are associated with prolonged recovery room stay, delayed discharge, and increased healthcare costs [3-5]. Procedures such as laparoscopy, gynecological surgery, and operations of longer duration are also associated with an increased incidence of PONV. Similarly, the use of general anesthesia and postoperative administration of opioid drugs contribute to a higher incidence of this complication [6, 7].

It is well established that conventional opioid drugs increase the risk of PONV in a dose-dependent manner [8]. Although the exact mechanisms by which opioid drugs cause nausea and vomiting are not yet fully understood, multiple mechanisms may be involved [9]. At the cellular level, traditional opioid agonists bind to the MOR and stimulate G protein signaling to produce analgesia, while activation of the β-arrestin pathway leads to adverse effects related to respiratory and gastrointestinal function [10]. In preclinical studies, β-arrestin-2 gene knockout mice treated with morphine exhibited enhanced analgesic effects and reduced respiratory depression and gastrointestinal dysfunction compared with wild-type animals treated with morphine [11, 12].

Oliceridine is a new generation intravenous opioid drug and a G protein-selective agonist. Oliceridine was approved for marketing in China in May 2023. In two randomized, double-blind, placebo- and morphine-controlled phase 3 pivotal studies, oliceridine provided rapid and effective analgesia with a favorable safety profile [13, 14]. In these two studies, the incidence of nausea in the 0.1 mg (40%) and 0.35 mg (59%) demand dose groups was lower than that in the morphine 1 mg group (70%), with the relative risk in the 0.1 mg demand dose group being 43% ($P<0.001$). The incidence of vomiting for oliceridine at three different required doses—0.1 mg (20%),

0.35 mg (30%), and 0.5 mg (42%)—was lower than that reported for morphine 1 mg (52%), with the relative risk for the 0.1 mg and 0.5 mg doses significantly reduced by 41%–61% ($P < 0.001$) [15, 16]. Hammer et al. [23] performed an exploratory analysis of these two trial datasets, defining the absence of vomiting and the non-use of rescue antiemetic medications as 'complete gastrointestinal response' as a composite endpoint. The analysis demonstrated that, compared to morphine, oliceridine achieved a 2–3-fold higher rate of 'complete gastrointestinal response' [16].

Gynecological surgical procedures predominantly involve the pelvic and abdominal cavities. Intraoperative mechanical traction and compression of pelvic and abdominal organs readily stimulate the vagus nerve and visceral afferent nerves, resulting in the release of central neurotransmitters that trigger PONV. It is noteworthy that with the widespread adoption of gynecological laparoscopic surgery, intraoperative pneumoperitoneum and the Trendelenburg position can increase intra-abdominal pressure, stimulating gastrointestinal emetic receptors and inducing PONV [17].

Oliceridine demonstrates safe and effective analgesic properties, with a marked advantage in gastrointestinal tolerability, which may support its rational application in gynecological surgery. This also constitutes the rationale for our research. However, oliceridine has only recently been introduced to the market, and there remains a lack of robust clinical evidence regarding its use in general anesthesia. Therefore, this study is designed as a randomized controlled trial, using sufentanil—a commonly used opioid drug in clinical practice—as the control, to compare the incidence of postoperative nausea and vomiting (PONV) following gynecological laparoscopic surgery.

2. Research Objectives

To explore the effects of oliceridine versus sufentanil on postoperative nausea and vomiting after gynecological laparoscopic surgery.

3. Research Protocol and Plan

3.1 Study Design

This study is a randomized, double-blind, parallel-controlled clinical trial to be conducted in the Department of Anesthesiology at the Second Xiangya Hospital of Central South University. Prior to initiation, the study will be approved by the hospital's medical ethics committee, and informed consent will be obtained from patients or their families. Patients will be randomized according to a computer-

generated randomization sequence into the sufentanil group and the oliceridine group. The sufentanil group will receive sufentanil for both anesthesia and postoperative analgesia, while the oliceridine group will receive oliceridine for both anesthesia and postoperative analgesia. Group allocation results are delivered to the anesthesia nurse using the sealed envelope method. Based on the study design and allocation, injection solutions with identical appearance and volume are prepared and provided to the attending anesthesiologist. The anesthesia nurse responsible for drug preparation does not participate in patient recruitment, randomization, data collection, or analysis.

3.2 Study Population

Inclusion criteria: Elective gynecological laparoscopic surgery; age 18–65 years; American Society of Anesthesiologists (ASA) physical status I–III; and body mass index (BMI) 18–30 kg/m².

Exclusion criteria: Severe dysfunction of major organs such as the heart, lungs, or brain; history of allergy to opioid drugs, propofol, soybeans, or eggs; recent use of sedatives, analgesics, or monoamine oxidase inhibitors; history of alcohol abuse; obstructive sleep apnea syndrome; difficult airway; psychiatric or neurological disorders; communication disorders; or women who are lactating or pregnant.

Withdrawal criteria: Subject requests withdrawal or withdraws voluntarily; change in surgical method requiring combined gastrointestinal surgery; occurrence of allergy to the investigational drug or life-threatening complications; or reoperation within 48 hours postoperatively due to bleeding or other factors.

3.3 Group Allocation and Interventions

Patients were randomly assigned to either the Sufentanil group or the Oliceridine group. No preoperative medications were administered. Upon entering the operating room, standard monitoring of ECG, SpO2, BP, and BIS was implemented, and intravenous access was established. Anesthesia induction: Sequential intravenous administration of midazolam 0.05–0.10 mg/kg, sufentanil 0.3 μg/kg (Sufentanil group) or oliceridine (0.06 mg/kg, based on the oliceridine injection package insert, where 1 mg oliceridine is approximately equivalent to 5 mg morphine), and propofol.1.5~2.0 mg/kg and cisatracurium besylate 0.2~0.3 mg/kg. Following intubation, both groups of patients underwent volume-controlled mechanical ventilation, with a tidal volume of 6~8 ml/kg, respiratory rate of 8~12 breaths/min, and an inspiratory-to-expiratory ratio of 1:2. Ventilation parameters were adjusted to maintain PCO2 at 35~40 mmHg (1 mmHg = 0.133 kPa). Prior to skin incision, patients received sufentanil 0.1–0.2

μg/kg (Sufentanil group) or oliceridine 0.02–0.04 mg/kg (Oliceridine group). Total intravenous anesthesia was maintained intraoperatively with continuous infusion of propofol at 4–10 mg/kg/h and remifentanil at 0.1–0.2 μg/kg/min, along with intermittent intravenous injections of cisatracurium besylate 4 mg. Approximately 30 minutes before the end of surgery, sufentanil 0.1 μg/kg (Sufentanil group) or oliceridine 0.02 mg/kg (Oliceridine group) was administered.

Postoperative analgesia protocol: The Sufentanil group received 2 μg/kg sufentanil, and the Oliceridine group received 0.4 mg/kg oliceridine. Ondansetron 8 mg and dexamethasone 10 mg were added to normal saline to a total volume of 100 ml. The initial loading dose was 2 ml, with no background infusion. Each bolus dose was 2 ml, the lockout interval was 10 minutes, and the maximum dose was 10 ml/h. All enrolled patients were connected to the electronic analgesia pump immediately after surgery, and patients and their families received preoperative instruction on the use of the electronic analgesia pump. If postoperative pain could not be alleviated by the analgesia pump, the anesthesiologist administered rescue sufentanil 5 μg or oliceridine 0.2 mg as needed. If rescue therapy is ineffective, the anesthesiologist will determine alternative remedial measures and document the medications and dosages administered. If the patient develops PONV of grade 2 or above, a combination of ondansetron 4 mg and dexamethasone 5 mg will be administered intravenously. If symptoms are not alleviated after one hour, haloperidol 1 mg will be administered in combination.

3.4 Outcome Measures and Follow-up Plan

Primary outcome measure: Incidence of PONV within 48 hours postoperatively. PONV will be assessed within 48 hours postoperatively in the ward by a blinded investigator. Subjects are required to use the simplified PONV impact scale to report whether any PONV events occurred in the past 48 hours and to provide a rating.

(Consisting of two questions: Q1. Have you experienced vomiting or symptoms of vomiting? If yes, how many episodes in total? Under what circumstances did it occur? Was any medication administered for treatment? Q2. Have you experienced nausea? If yes, did the sensation of nausea affect your daily activities? Was any medication administered for treatment?) Based on the number, frequency, and triggers of nausea and vomiting, the incidents are classified into four grades: absence of vomiting or nausea not requiring rescue treatment after onset is defined as complete remission; Mild PONV is defined as mild nausea or a single episode of vomiting

induced by drinking water or physical activity. Moderate PONV is defined as two episodes of vomiting or significant nausea requiring rescue therapy. Severe PONV is defined as more than two episodes of vomiting or the need for more than one dose of rescue therapy.

General patient data: including age, height, weight, BMI, ASA classification, smoking history, previous history of PONV, history of motion sickness, surgical history, history of hypertension, history of diabetes, among others.

Intraoperative indicators: surgical method, surgical site, blood loss, operative duration, anesthesia duration, anesthetic dosage, infusion volume, and incidence of hypotension.

Secondary outcome measures:

1) Record the occurrence of PONV separately for four time periods (T1: PACU stay; T2: from departure from PACU to 12 hours postoperatively; T3: 12 to 24 hours postoperatively; T4: 24 to 48 hours postoperatively). Incidence of postoperative vomiting (POV) and POV scores during the four time periods (T1–T4) within 48 hours after surgery. Record the use of rescue antiemetic medications.

Postoperative analgesia assessment: Resting visual analog scale (VAS) pain scores at four time points (T1–T4) within 48 hours after surgery, measured using a 10 cm movable ruler with a numerical scale of 0–10 on the reverse side. The left end (“0”) indicates no pain, while the right end (“10”) represents unbearable severe pain. Record the number of PCA presses, total analgesic consumption, and the use of rescue analgesics within 48 hours after surgery.

Ramsay sedation score at 2 hours postoperatively: a score of 1 indicates agitation, 3 or 4 indicates somnolence, and 5 or 6 indicates excessive sedation.

Sleep quality score on the night after surgery: Patient sleep quality will be assessed using a numerical rating scale based on an 11-point Likert scale, ranging from 0 to 10. A score of 0 indicates complete insomnia and extremely poor sleep quality, while a score of 10 represents excellent sleep quality. Severe insomnia is defined as a score of 0–3, moderate insomnia as 4–6, and good sleep quality as 7–10.

QOR-15 score: A score of 0 indicates extremely poor quality of recovery, while a score of 150 indicates excellent quality of recovery. Assessments will be conducted preoperatively, on postoperative day 1, and on postoperative day 3.

Length of stay in the recovery room, time to first postoperative bowel movement, time to resumption of oral intake, time to first postoperative feeding, time to first

postoperative ambulation, and any other adverse events.

3.5 Statistical Analysis Plan

Sample size calculation: The primary outcome is the incidence of PONV within 48 hours postoperatively, and the sample size will be calculated based on this primary endpoint. According to the study by Zhao et al., the incidence of PONV within 48 hours after gynecological laparoscopic surgery is 71.7%. It is expected that the incidence of PONV will be reduced by at least 40%. Assuming $\alpha = 0.05$ and a power of 80%, PASS 15 software was used to calculate a sample size of N = 45 per group. Considering a 5% dropout rate, a total of 48 patients per group will be enrolled, requiring 96 subjects in total.

Statistical analysis was conducted using SPSS 26.0. Normally distributed continuous data were expressed as mean ± standard deviation (mean ± SD), and between-group comparisons were performed using the independent samples t-test. Non-normally distributed continuous data were expressed as median (M) and interquartile range (IQR), and between-group comparisons were performed using the Wilcoxon rank-sum test. Repeated measures data were analyzed using repeated measures analysis of variance or the generalized estimating equation model, according to the distribution characteristics of the data. Categorical data were expressed as rates or percentages, and comparisons were performed using the $\chi 2$ test or Fisher's exact test. Ordinal data were analyzed using the rank-sum test. Subgroup analyses will be performed based on operative duration (≤2h or >2h), smoking status (non-smoker or history of smoking within the past six months), history of chemotherapy, age (≤50 or >50), and BMI (18-25 or 25-30), using logistic regression analysis. A P value <0.05 will be considered statistically significant.

4. Data Management and Quality Control

All drugs and materials used in the clinical research must be subjected to quality control. Researchers or relevant medical management authorities are entitled to audit the clinical research to ensure the authenticity of recorded data and compliance with the clinical research protocol.

This study is an investigator-initiated clinical trial and will adhere to the standards and requirements of the Good Clinical Practice (GCP) guidelines and ICH-GCP regulations. At the project initiation stage, the principal investigator is responsible for designing and developing the study protocol, case report forms, and other relevant documents, and will submit the necessary application materials for

project approval in accordance with the requirements of the hospital's administrative office. After obtaining the project number from the institutional office, the project materials will be submitted to the Ethics Office for ethical review. Upon completion of the ethical review, the project will be registered with the administrative office in preparation for implementation.

During the implementation of the project, all researchers participating in the trial will obtain GCP qualification certificates. Researchers shall conduct the clinical trial in accordance with relevant Chinese GCP, ICH-GCP, and related SOPs. During project quality management, the principal investigator authorizes the quality control officer to conduct monthly project quality control, completing the 'Clinical Trial Quality Control Checklist for Project Teams' to ensure that the clinical trial is conducted in accordance with GCP and protocol requirements. Upon completion of the project, the principal investigator shall issue a formal 'Project Closure Letter' to the Ethics Office and the institutional office. At project conclusion, the principal investigator is responsible for organizing and preserving the research data. A hard copy of the 'Study Completion Report' shall be submitted to the Ethics Office, and the principal investigator shall be responsible for the authenticity of the report.

5. Risks and Benefits

The oliceridine package insert clearly indicates that it is approved for the treatment of acute pain in adult patients severe enough to require intravenous opioid drugs. As intraoperative pain in adult gynecological surgery necessitates the use of opioid drugs for management, the application of oliceridine injection for acute pain in gynecological surgery is consistent with the approved indications. Oliceridine not only provides safe and effective analgesia, but also offers significant advantages in gastrointestinal tolerability. Currently, this drug has been successfully tendered and stocked in our hospital pharmacy, enabling its rational application in gynecological surgery and thereby improving perioperative comfort for gynecological patients.

The social benefits and subject gains from this study are reflected in the following aspects:

Social benefits:

(1) Improvement of patients' postoperative experience: By effectively controlling postoperative pain and reducing severe vomiting, this approach can significantly enhance overall patient satisfaction, shorten hospital stays caused by pain and vomiting, and reduce the consumption of medical resources.

(2) Promotion of clinical drug innovation: This study will provide scientific evidence for the clinical application of oliceridine, facilitate the broader adoption of new-generation opioid drugs in the field of gynecology, and offer patients safer and more effective analgesic regimens.

(3) Promotion of medical research and development: This study will facilitate further exploration of opioid drugs in various types of surgical procedures,

enhance understanding of the safety and efficacy of anesthetic agents, and promote advances in anesthesiology and related fields.

Benefits to Subjects

(1) Economic benefit: Subjects will be exempted from perioperative anesthesiology pain assessment fees (clinical scale), valued at 36 yuan.

Effective analgesia management: Subjects participating in this study will receive oliceridine, which may provide superior analgesic effects, improve postoperative recovery quality, and reduce postoperative discomfort.

(2) Reduction of severe vomiting: This study aims to evaluate the efficacy of oliceridine in reducing postoperative severe vomiting, which is critical for postoperative recovery and can enhance patients' quality of life.

(3) Participation in cutting-edge research: Subjects will have the opportunity to take part in advanced medical research, providing real-world clinical data for the application of new medications and contributing to future medical progress.

6. Safety Assessment and Risk Management Measures

According to the procedures for handling emergency medical adverse events during the subject’s hospitalization (including the ICU period):

(1) When a subject experiences harm or an unexpected event, medical staff should immediately report to the resident physician or on-duty physician. The resident physician or on-duty physician should implement appropriate emergency measures based on the patient's condition and immediately notify the discipline lead and principal investigator (the discipline lead and principal investigator may be the same individual), as well as the assistant researcher (authorized by the principal investigator and holding the title of attending physician or above). Upon receiving the report, the discipline lead, principal investigator, and assistant researcher should personally participate or assign a senior physician to assist in managing the situation in the ward within 15 minutes. If the situation is extremely critical, it may be necessary to coordinate with anesthesiologists and ICU physicians for resuscitation.

(2) While managing the event, the resident physician or on-duty physician must ensure that the clinical trial investigator records the subject's symptoms, severity, time of onset, duration, interventions, and clinical course in the medical record and observation form within 12 hours. (3) The principal investigator or assistant researcher must report the emergency medical adverse event to the secretary of the drug clinical trial institution office within 12 hours, and, if necessary, may report directly to the institution director or office director.

(4) The investigator may decide to terminate trial observation based on the subject's condition, or adjust the trial medication dosage only/ temporarily suspend the study. In the event of a serious adverse event or important adverse event requiring emergency unblinding, the investigator shall immediately notify the sponsor and the institutional quality control officer, perform unblinding in accordance with the protocol requirements and unblinding SOP, and document the unblinding process in detail.

Subjects who experience a serious adverse event shall be observed and followed until symptoms, signs, and relevant laboratory tests return to normal, and the relevant departments shall be notified within 24 hours in accordance with GCP and protocol requirements. In the event of a medical dispute or related tendency, refer to the Emergency Plan for Hazards to Hospital Public Order of The Second Xiangya Hospital of Central South University.

References:

[1] Fourth Consensus Guidelines for the Management of Postoperative Nausea and Vomiting: Erratum [J]. Anesth Analg, 2020, 131(5): e241. 10.1213/ane.0000000000005245

[2] Habib AS, Chen YT, Taguchi A, et al. Postoperative nausea and vomiting following inpatient surgeries in a teaching hospital: a retrospective database analysis [J]. Curr Med Res Opin, 2006, 22(6): 1093-1099. 10.1185/030079906x104830

[3] Andrew BY, Holmes R, Taicher BM, et al. The Association of Guideline-Directed Prophylaxis With Postoperative Nausea and Vomiting in Adult Patients: A Single-Center, Retrospective Cohort Study [J]. Anesth Analg, 2024. 10.1213/ane.0000000000006855

[4] Apfel CC, Korttila K, Abdalla M, et al. A factorial trial of six interventions for the prevention of postoperative nausea and vomiting [J]. N Engl J Med, 2004,

350(24): 2441-2451. 10.1056/NEJMoa032196

[5] Zhu H, Wang S, Wang R, et al. Effect of dexmedetomidine on postoperative nausea and vomiting in female patients undergoing radical thoracoscopic lung cancer resection [J]. Front Pharmacol, 2024, 15: 1353620. 10.3389/fphar.2024.1353620

[6] Gan TJ, Belani KG, Bergese S, et al. Fourth Consensus Guidelines for the Management of Postoperative Nausea and Vomiting [J]. Anesth Analg, 2020, 131(2): 411-448. 10.1213/ane.0000000000004833

[7] Xue FS, Su K, Cheng Y. Opioid-free anaesthesia reduces postoperative nausea and vomiting after thoracoscopic lung resection. Comment on Br J Anaesth; 132: 267-76 [J]. Br J Anaesth, 2024, 132(4): 827-828. 10.1016/j.bja.2024.01.022

[8] Roberts GW, Bekker TB, Carlsen HH, et al. Postoperative nausea and vomiting are strongly influenced by postoperative opioid use in a dose-related manner [J]. Anesth Analg, 2005, 101(5): 1343-1348. 10.1213/01.ane.0000180204.64588.ec

[9] Smith HS, Smith JM, Seidner P. Opioid-induced nausea and vomiting [J]. Ann Palliat Med, 2012, 1(2): 121-129. 10.3978/j.issn.2224-5820.2012.07.08

[10] Rankovic Z, Brust TF, Bohn LM. Biased agonism: An emerging paradigm in GPCR drug discovery [J]. Bioorg Med Chem Lett, 2016, 26(2): 241-250. 10.1016/j.bmcl.2015.12.024

[11] Raehal KM, Walker JK, Bohn LM. Morphine side effects in beta-arrestin 2 knockout mice [J]. J Pharmacol Exp Ther, 2005, 314(3): 1195-1201. 10.1124/jpet.105.087254

[12] Bohn LM, Lefkowitz RJ, Gainetdinov RR, et al. Enhanced morphine analgesia in mice lacking beta-arrestin 2 [J]. Science, 1999, 286(5449): 2495-2498. 10.1126/science.286.5449.2495

[13] Viscusi ER, Skobieranda F, Soergel DG, et al. APOLLO-1: a randomized placebo and active-controlled phase III study investigating oliceridine (TRV130), a G protein-biased ligand at the μ-opioid receptor, for management of moderate-to-severe acute pain following bunionectomy [J]. J Pain Res, 2019, 12: 927-943. 10.2147/jpr.s171013

[14] Singla NK, Skobieranda F, Soergel DG, et al. APOLLO-2: A Randomized, Placebo and Active-Controlled Phase III Study Investigating Oliceridine (TRV130), a G Protein-Biased Ligand at the μ-Opioid Receptor, for Management of Moderate to Severe Acute Pain Following Abdominoplasty [J]. Pain Pract, 2019, 19(7): 715-731.

10.1111/papr.12801

[15] Beard TL, Michalsky C, Candiotti KA, et al. Oliceridine is Associated with Reduced Risk of Vomiting and Need for Rescue Antiemetics Compared to Morphine: Exploratory Analysis from Two Phase 3 Randomized Placebo and Active Controlled Trials [J]. Pain Ther, 2021, 10(1): 401-413. 10.1007/s40122-020-00216-x

[16] Hammer GB, Khanna AK, Michalsky C, et al. Oliceridine Exhibits Improved Tolerability Compared to Morphine at Equianalgesic Conditions: Exploratory Analysis from Two Phase 3 Randomized Placebo and Active Controlled Trials [J]. Pain Ther, 2021, 10(2): 1343-1353. 10.1007/s40122-021-00299-0

[17] Zhao K, Gao Y, Zhang J, et al. Penehyclidine for Prevention of Postoperative Nausea and Vomiting in Patients Undergoing Gynecological Laparoscopic Surgery Under Combined Intravenous and Inhalation Anesthesia: A Randomized, Double-Blind, Placebo-Controlled Trial [J]. Drug Des Devel Ther, 2024, 18: 685-697. 10.2147/dddt.s453327