

RETRACTED ARTICLE: Effective Doses of Oliceridine Combined with Propofol for Painless Hysteroscopy: A Prospective Dose-Finding Study

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Background: The combination of oliceridine with propofol represents a new option for complete intravenous anesthesia in painless hysteroscopy. The purpose of this study was to determine the 95% effective dose (ED95) and the median effective dose (ED50) of oliceridine when combined with propofol for painless hysteroscopy.

Methods: A total of 29 patients, aged between 18 and 60 years and classified as American Society of Anesthesiologists (ASA) I–II, were initially recruited for hysteroscopy. Subsequently, 26 of these patients were included in the final analysis. Before surgery, an intravenous dose of 0.02 mg/kg oliceridine, with a dose gradient of 0.002 mg/kg, was administered using Dixon's up-and-down method. Two minutes later, 2 mg/kg of propofol was administered. The oliceridine dosage for the following patient was increased by 0.002 mg/kg if the hysteroscopy failed (defined as poor cervical dilatation, problematic hysteroscopic placement, or a Ramsay Sedation Scale (RSS) score < 5 or any movement and frowning by the patient within 5 minutes). In contrast, the dosage was decreased by 0.002 mg/kg. At least seven crossovers had to occur before the test was stopped. The ED50 and ED95 of oliceridine in combination with propofol for hysteroscopy were determined using the probit analysis method.

Results: The ED50 and ED95 of oliceridine and 95% CI were 0.0192 (0.0183–0.0216) mg/kg and 0.0237 (0.0214–0.0415) mg/kg, respectively. No patients experienced significant adverse effects.

Conclusion: The study determined that the ED50 and ED95 of oliceridine in combination with propofol for painless hysteroscopy are 0.0192 mg/kg and 0.0237 mg/kg, respectively. Oliceridine at 0.0237 mg/kg provides safe and effective anesthesia when combined with propofol.

Keywords: oliceridine, propofol, hysteroscopy, effective dose, ED50, ED95

Introduction

The most popular method for gynecological diagnosis and treatment is hysteroscopy, which offers accurate and intuitive assessments of intrauterine lesions and hemorrhagic illnesses. Without anesthesia, this procedure can be performed in outpatient clinics. However, the majority of patients cannot tolerate the severe pain caused by cervical canal dilatation without adequate analgesia and sedation.^{1–3} The type of operation, patient tolerance, and the complexity of the intervention are some of the criteria that influence the anesthetic decision for hysteroscopy. For diagnostic hysteroscopy, non-pharmacological pain management techniques, including modifying the filling pressure of the uterus, or local anesthetic may be adequate. This approach has been shown to reduce pain levels during the procedure, as demonstrated in a study by Terkan et al.⁴ For more complex operative hysteroscopy, general anesthesia or deep sedation may be required to ensure patient comfort and facilitate surgical precision. However, local anesthetics and other minimally invasive pain management methods should also be taken into account.^{5,6} The particular requirements of each patient and

the requirements of the procedure should guide the choice of anesthetic. Intravenous anesthesia without tracheal intubation has become increasingly popular for hysteroscopy procedures in recent years.^{7,8} Propofol, known for its rapid onset, short duration of action, and minimal side effects, is frequently used to induce and maintain anesthesia during hysteroscopic surgery.⁹ However, propofol's poor analgesic efficacy and potential negative cardiovascular effects necessitate its combination with other analgesics.¹⁰

Oliceridine is a novel G protein-biased μ -opioid receptor agonist that selectively activates G-protein signaling while reducing the recruitment of β -arrestin.¹¹ Analgesia is related with G-protein signaling, whereas negative effects are linked to β -arrestin recruitment, indicating a wider treatment window.^{12,13} Therefore, oliceridine is increasingly being used for hysteroscopy analgesia.

However, the optimal minimal effective dosage of oliceridine in combination with propofol for hysteroscopy procedures remains to be determined. This study aimed to determine the median effective dose (ED50) and 95% effective dosage (ED95) of oliceridine in combination with propofol for painless hysteroscopy.

Methods

Study Design

Approved by the Cixi People's Hospital Ethical Committee in Cixi, China, this dose-finding study was registered in the Chinese Clinical Trial Registry (www.chictr.org.cn; registration number CTR240001657). Prior to enrollment, written informed consent was given by each participant.

Patients

From December 2024 to January 2025, we recruited 26 patients, ages 18 to 60, with American Society of Anesthesiologists (ASA) physical status of I or II who were scheduled for painless hysteroscopy under intravenous anesthetic at our institution. The following were excluded: ASA class III or above; age <18 or >60 years; liver or renal dysfunction or other systemic issues prior to the operation; disease of the central nervous, respiratory, or circulatory systems; psychotic disorders; escalation to tracheal intubation and general anesthesia; and a procedure lasting longer than 30 minutes.

Anesthesia Protocol

Before surgery, patients received no premedication, were fasted for eight hours, and had venous access established in the left upper limb upon entering the operating room. Routine monitoring included blood pressure, pulse oximetry (SpO₂), and electrocardiogram, and supplemental oxygen was delivered via a mask at 5 L/min. This research used Dixon's up-and-down method. Prior to the procedure, oliceridine (Jiangsu Enhua Pharmaceuticals Co. Ltd., China) was administered intravenously. The initial dosage, which was determined by preliminary experimentation and previously published studies, was 0.02 mg/kg.¹⁴ After 2 min after the onset, 2mg/kg of propofol (Jiangsu Yangtze River Pharmaceuticals Co. Ltd., China) was gradually injected over at least one minute. After the patient lost consciousness and the eyelash reflex, a skilled gynecologist performed a hysteroscopy. In the event that the hysteroscopy failed (characterized by poor cervical dilatation, difficult hysteroscopic placement, or a Ramsay Sedation Scale (RSS) score < 5, or any movement and frowning by the patient within 5 minutes), an additional 0.5 mg/kg of propofol was administered intravenously. In this instance, the oliceridine dosage was raised by one dose gradient for the subsequent patient. On the other hand, if the examination was successful, the dose gradient for the following patient was reduced by one dose gradient. There was a 0.002 mg/kg difference between the two nearby dosages. Seven crossings were thought to be adequate in this study to determine the oliceridine's ED50/ED95.

The Ramsay Sedation Scale¹⁵ was scored on a 6-point scale as follows: Level 1: the patient is irritable, restless, or anxious; Level 2: the patient is quiet, cooperative, and well-organized; Level 3: the patient reacts only to commands; Level 4: the patient reacts rapidly to intense sound stimulation or tapping of the eyebrows; Level 5: the patient is unresponsive to these stimuli; Level 6: the patient is completely unresponsive.

The oliceridine dosage, the initial and total doses of propofol, the inspection time (from insertion to withdrawal of the hysteroscope), and the anesthetic recovery time (from the last propofol administration to patient recovery) were recorded. The visual analogue scale (VAS) pain score was measured during the anesthesia recovery period. Scores ranging from 0 to 10 indicate varying levels of pain, with 0 denoting no pain and 10 denoting severe pain. Mean arterial pressure (MAP) and heart rate (HR) were also measured prior to induction (T1), at the start of operation (T2), and at the time of recovery (T3).

The following adverse effects were recorded: bradycardia (HR < 50 beats/min), respiratory depression (RR < 6 breaths/min or hypoxemia (SpO₂ < 90%)), and hypotension (mean blood pressure > 20% drop from the baseline MBP or systolic blood pressure < 90 mmHg). Atropine (0.3–0.5 mg) and ephedrine (5–10 mg) were used to treat bradycardia and hypotension, respectively. When respiratory depression occurred, the lower jaw was supported to facilitate breathing. If the SpO₂ level failed to increase or continued to decline, mask pressure-assisted ventilation was initiated. Additionally, drowsiness, nausea, and vomiting were frequently observed as common adverse effects during the recovery of anesthesia.

Statistical Analysis

In accordance with the up-down sequential method's stop rule,^{16,17} the simulation study's results indicated that 20–40 patients would yield consistent estimates of ED₅₀/ED₉₅, therefore a sample size of 26 patients was chosen for this investigation. SPSS 25.0 (SPSS Inc., Chicago, IL, USA) was used for all statistical analyses. The independent samples Student's *t*-test was used to compare normally distributed data at several time intervals, and the results were presented as means ± standard deviation. The probit approach (probability unit regression) was used to determine the oliceridine's ED₅₀/ED₉₅ and 95% CI when combined with propofol. *P* < 0.05 was deemed statistically significant.

Results

All 26 participants who were enrolled finished the study. Figure 1 depicts the patient enrollment flowchart. Table 1 provides a summary of the participants' demographic details. Table 2 displays the patient perioperative profiles. One patient had drowsiness, whereas only two patients experienced temporary respiratory depression. Throughout the procedure, every hemodynamic index remained stable. Compared to T1, the MAP and HR at T2 were considerably lower (MAP 92.78 ± 11.24 vs 76.39 ± 11.46; HR 72.15 ± 13.17 vs 67.51 ± 10.89, *P* < 0.05) (Table 3).

Figure 2 displays the sequential of effective and ineffective doses of oliceridine combined with propofol for painless hysteroscopy. According to the up-and-down sequential allocation method, the ED₅₀ of oliceridine was 0.0192 mg/kg (95% CI 0.0183–0.0216), and the ED₉₅ was 0.0237 mg/kg (95% CI 0.0214–0.0415).

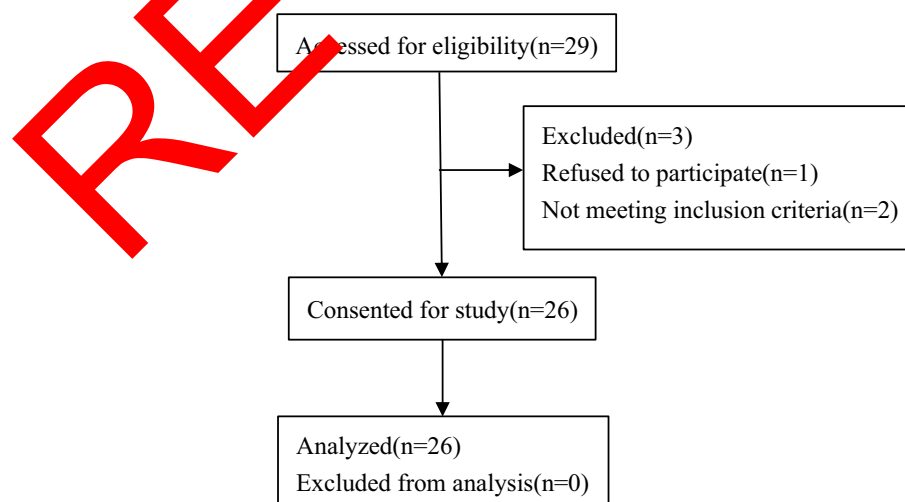


Figure 1 Flow diagram of the study.

Table 1 Demographic Characteristics of Patients

Demographic Data	Mean ± SD
Age (years)	36.31 ± 8.24
Height (cm)	160.17 ± 4.69
Weight (kg)	58.5 ± 6.38
BMI (kg/m ²)	22.39 ± 2.06

Note: Values are presented as the mean ± SD.
Abbreviations: BMI, body mass index; SD, standard deviation.

Table 2 Perioperative Profiles of the Patients

Index	Mean ± SD
Dose of oliveridine (mg)	0.94 ± 0.81
Initial dose of propofol (mg)	105.63 ± 12.84
Total dose of propofol (mg)	164.52 ± 31.47
Inspection time (min)	10.21 ± 4.32
Time of recovery (min)	5.16 ± 2.37
VAS pain score (points)	1.58 ± 0.62
Respiratory depression (n)	2
Nausea and vomiting (n)	1
Drowsiness (n)	1

Note: Values are presented as the mean ± SD or the number of patients.
Abbreviations: VAS, visual analogue scale; SD, standard deviation.

Table 3 Haemodynamic Parameters at Different Time Points

Index		T2	T3
Heart rate (b/min)	75.65 ± 13.17	67.51 ± 10.89*	72.74 ± 11.35
Mean arterial pressure (mmHg)	92.78 ± 11.24	76.39 ± 9.46*	87.43 ± 8.54

Note: Values are presented as the mean ± standard deviation. T1, time before induction; T2, at the start of the operation; T3, at the time of recovery. *P <0.05, compared with T1.

Discussion

One crucial technique for the identification and management of uterine disorders is hysteroscopy. The choice of anesthesia for office hysteroscopy depends on the procedure type, patient characteristics, and pain tolerance.^{1,6} For simple diagnostic procedures, local anesthesia or non pharmacological methods like adjusting uterine cavity filling pressure can be effective. These options provide sufficient pain relief with minimal side effects. For more complex or longer procedures, sedation or even general anesthesia may be necessary to ensure patient comfort and procedural success. Ultimately, the choice of anesthesia must be customized to meet the individual needs and preferences of each patient, while carefully balancing safety and efficacy.^{4,5}

Propofol and opioids continue to be the most commonly used intravenous anesthetics for hysteroscopy.¹ The analgesic effect of propofol is mild, whereas opioids like sufentanil and fentanyl are more likely to have side effects.^{3,18} Even though painless hysteroscopy is believed to be a safe and well-tolerated technique, anesthesiologists have always faced challenges in preserving patients' stable respiratory function and lowering the incidence of side effects.¹⁵

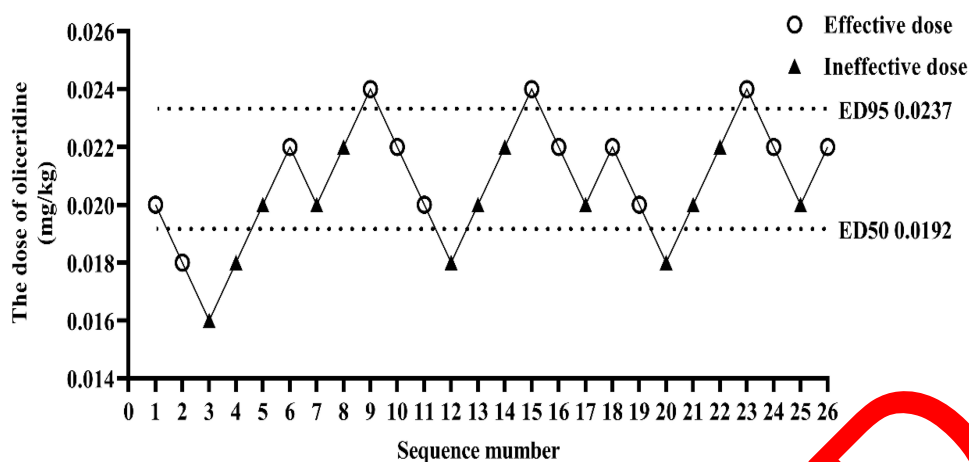


Figure 2 For painless hysteroscopy, oliceridine dosage is gradually adjusted using Dixon's up-and-down method. A circle indicates an effective dosage, while a filled triangle indicates an ineffective one.

Abbreviations: ED50, median effective dose; ED95, 95% effective dose.

Oliceridine, a new μ -opioid receptor agonist, selectively activates the β -arrestin and G-protein signaling pathways.¹¹ By stimulating merely G protein signaling and not β -arrestin recruitment, selective μ -opioid receptor agonists may provide analgesic advantages with fewer side effects.

Oliceridine is a new type of opioid that provides effective pain relief while causing significantly fewer complications such as respiratory depression than traditional opioids.^{19,20}

Oliceridine offers faster onset of action, improved tolerance, fewer side effects, and lower addiction potential compared to morphine. These advantages ultimately reduce long-term treatment costs for patients, making it a promising alternative to traditional opioid therapies.^{6,19,21}

With less cardiovascular inhibition than other analgesic anesthetics, these qualities make it a perfect complement to propofol.^{11,12,18} The combination of oliceridine and propofol has the potential to provide optimal sedation and analgesia while reducing the incidence of associated complications.

However, there are few reports on the use of oliceridine in painless hysteroscopy. Therefore, determining the ED50 and ED95 of oliceridine when combined with propofol is essential for establishing a rational basis for clinical medication use. Based on previous studies, patients with chronic non-cancer pain safely and effectively tolerated oliceridine, which demonstrated rapid analgesic onset within 1 to 2 minutes, peak efficacy at 6 to 12 minutes, and a half-life of 1.3 to 3 hours, across a dosing range of 0.75 mg to 3.0 mg. Consequently, the initial oliceridine dosage in this trial was established at 0.02 mg/kg and was given two minutes before the propofol injection. The test was conducted with a predetermined iso-effectual concentration of 0.002 mg/kg until at least seven crossovers were obtained. The ED50 and ED95 values of oliceridine with propofol (2 mg/kg) for intravenous sedation in painless hysteroscopy were obtained in an up-and-down sequential allocation dose-finding study to be 0.0192 (95% CI 0.0183–0.0216) mg/kg and 0.0237 (95% CI 0.0224–0.0415) mg/kg, respectively.

The findings also demonstrated that oliceridine and propofol were safe for use in hysteroscopy procedures. None of the patients experienced nausea or vomiting. Only two patients experienced brief respiratory depression, and one patient developed drowsiness. The incidence of respiratory depression, nausea, and vomiting is decreased because oliceridine agonizes the action of μ -receptors and has decreased engagement of the β -arrestin pathway, which is linked to negative consequences.²² Although the MAP and HR at the T1 and T2 time points differed significantly, they were still within 20% of the baseline value at the T2 time point. Previous research has demonstrated that oliceridine has no direct effect on the circulatory system. Propofol may have had an impact on these outcomes.^{11,22} The patients' mean VAS pain score at the time of recovery was 1.58 ± 0.62 , which was regarded as mild pain and suggested that oliceridine had a potent analgesic effect. Gynecologists and patients expressed satisfaction with the surgical process.

There were some limitations to this study. First, the small sample size inherent to Dixon's up-and-down method may introduce selection bias. A larger, multi-center study is needed to validate these results. Second, the estimated dosages for propofol and oliceridine only apply to patients with ASA I–II status; further studies are needed to determine appropriate dosages for patients with more severe comorbidities (ASA III–IV). Third, using only the Ramsay Sedation Scale instead of more objective measures like the bispectral index or electroencephalogram monitoring may have introduced bias into the assessment of sedation levels.

Conclusion

Our study established that the ED50 and ED95 of oliceridine in combination with propofol for painless hysteroscopy anesthesia are 0.0192 mg/kg and 0.0237 mg/kg, respectively. Therefore, we recommend using oliceridine at a dose of 0.0237 mg/kg in combination with propofol to achieve safe and effective painless hysteroscopy in adult patients.

Data Sharing Statement

The supporting data for this study can be obtained from the corresponding author upon reasonable request.

Ethics Approval and Informed Consent

Ethical permission was granted by the Cixi People's Hospital ethics committee in November 2024. All procedures were conducted in accordance with the Declaration of Helsinki, and each patient provided their informed consent.

Acknowledgments

We are especially grateful to our colleagues in the Cixi People's Hospital Gynecology Department for their contributions to this study.

Funding

A grant from the Gusu Health Talent Program (grant number, G2023013) provided funding for this investigation.

Disclosure

The authors disclose that they have no conflicting financial or personal interests with regard to this manuscript's publication.

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