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CLINICAL TRIAL REPORT

# Determination of the 90% Effective Dose of Oliceridine Combined with Propofol for Day-Case Hysteroscopy

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**Purpose:** This study employed probit regression analysis to determine the 90% effective dose ($ED_{90}$) of oliceridine when combined with propofol for day-case hysteroscopy.

**Patients and Methods:** 100 patients undergoing hysteroscopic surgery were randomized to receive intravenous oliceridine (0.01, 0.015, 0.02, 0.025, or 0.03 mg $kg^{-1}$) 3 minutes preoperatively. Propofol was administered intravenously at 2 mg $kg^{-1}$ induction and maintained at 6 mg $kg^{-1}$ $h^{-1}$. Successful anesthesia was defined as absence of body movement during cervical dilation. Parameters recorded included the success rate, propofol consumption, total surgical duration, recovery time, postoperative pain, and adverse events.

**Results:** The $ED_{90}$ of oliceridine for suppressing response to cervical dilation was 0.025 (95% confidence interval, CI, 0.020–0.050) mg $kg^{-1}$. The incidence of propofol injection pain in the 0.01, 0.015, 0.02, 0.025, and 0.03 mg $kg^{-1}$ oliceridine groups (80%, 80%, 45%, 40%, and 30%, respectively) were significantly different (P = 0.001). There was no difference in the propofol requirements, time to anesthesia emergence, and visual analog scores(VAS) at 30 minutes postoperation among groups. No serious adverse events occurred in any patient.

**Conclusion:** For healthy adult women undergoing day-case hysteroscopy, oliceridine 0.025 mg $kg^{-1}$ combined with propofol provides effective and safe anesthesia.

**Keywords:** oliceridine, dose-response, 90% effective dose, $ED_{90}$, hysteroscopy

## Introduction

Hysteroscopy is a diagnostic and minimally invasive surgical treatment method for various lesions in the uterine cavity and cervical canal through the natural vaginal orifice, which is considered the gold standard for diagnosing and treating intrauterine diseases.[1,2] For some individuals, hysteroscopy can cause significant pain.[3] Approximately 17.6% of patients report pain scores exceeding 7 (on a 0–10 scale, 0 = no pain and 10 = most severe pain) during hysteroscopy, with an average pain score of 3.9.[4] Notably, over 30% of patients undergoing mini-hysteroscopy still experience pain scores greater than 4.[5] Given that the procedure can be painful, providing effective pain management is crucial.

In 2021, a total of 268 medical centers in mainland China conducted 552,225 hysteroscopies. The average proportion of hysteroscopy conducted under general anesthesia was 63.8%, with 47.3% of medical institutions having an anaesthesia percentage of exceeding 75%. Propofol combined with opioid analgesics, including fentanyl (87.9%), sufentanil (62.8%), and remifentanil (32.1%), were the most commonly used intravenous anesthetics.[6] While oliceridine is a novel μ-opioid receptor agonist approved by the United States Food and Drug Administration (FDA) on August 7, 2020, as the world's



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first and only marketed biased μ-opioid receptor agonist. The clinical evidence for its use is currently limited. Distinct from the structural architectures of morphine, fentanyl, and other μ-opioid receptor agonists, oliceridine selectively activates the G protein signaling pathway (producing analgesic effects) while downregulating the agonistic activity of β-arrestin (associated with opioid-related adverse effects).[7] This mechanism may reduce the occurrence of opioid-related adverse events (ORAE), particularly respiratory depression and gastrointestinal complications,[8] meeting the demand for analgesics that retain the efficacy of traditional opioids but with fewer side effects. Its application in hysteroscopy offers certain advantages over other opioids.

Propofol-opioid combinations represent the most widely utilized intravenous anesthesia regimen for day-case surgeries.[9–13] With increasing demand for optimized anesthesia in ambulatory hysteroscopy, the dose-response relationship of oliceridine in this context remains undefined, necessitating formal dose-finding studies. This investigation aimed to determine both the 90% effective dose of oliceridine compounded with propofol for successful hysteroscopic procedures and evaluate its clinical feasibility through pharmacodynamic and safety assessments.

# Material and Methods

## Ethics and Registration

The protocol was approved by the Research Ethics Committee of Zhejiang Xiaoshan Hospital (No. KL2025004PJ) and registered in the Chinese Clinical Trial Registry (https://www.chictr.org.cn No. ChiCTR2500101669). The double-blind, randomized study was executed in compliance with the Declaration of Helsinki, from March 3, 2025, through May 10, 2025. Written informed consent was procured from all participants.

## Patient Eligibility

Women scheduled to undergo operative hysteroscopy under intravenous anesthesia were assessed for study eligibility. Patients aged 18–55 with American Society of Anesthesiologists (ASA) physical status of I or II and body mass index (BMI) 18–25kg $m^{-2}$ were recruited. Exclusion criteria included any of the following conditions: (1) cardiopulmonary diseases, including electrocardiogram (ECG) abnormalities (QTc interval of >470 milliseconds); (2) pregnant or lactating women; (3) hepatic or renal insufficiency; (4) obstructive sleep apnea-hypopnea syndrome (OSAHS); (5) chronic use of medications potentially affecting analgesic responses (central α-adrenergic agents, anticonvulsants, neuroleptics, antidepressants, antipsychotics); (6) allergy to opioids or anesthetics such as propofol; (7) risk of aspiration; (8) difficult cervical dilation, defined as cervical dilation duration exceeding 5 minutes.

## Randomization and Blinding

The computer-generated random numbers were concealed in sequentially numbered, opaque envelopes. An assistant not involved in the study procedures opened each envelope according to the recruitment sequence prior to anesthesia and prepared the study medication in identical 20 mL syringes labeled only with the study serial number.Enrolled patients were randomly assigned to one of five dose groups: 0.01, 0.015, 0.02, 0.025, and 0.03 mg $kg^{-1}$ of oliceridine. The anesthesiologists responsible for data collection and evaluation, as well as the patients and researchers, remained blinded to group allocation throughout the study.

## Anesthetic Procedure

All patients were instructed to fast from solid foods for 8 hours and clear fluids for 2 hours preoperatively. Upon entering the operating room, intravenous access was established for each patient. Routine monitoring was performed at 3-minute intervals, including non-invasive blood pressure (NIBP), ECG, and peripheral oxygen saturation ($SpO_2$), with all parameters being systematically documented. All patients received oxygen via nasal cannula at a flow rate of 5L $min^{-1}$.

Patients were randomly assigned (20 per group) to one of five different doses of oliceridine (Jiangsu Nhwa Pharmaceuticals Co. Ltd., China): 0.01 mg $kg^{-1}$, 0.015 mg $kg^{-1}$, 0.02 mg $kg^{-1}$, 0.025 mg $kg^{-1}$, or 0.03 mg $kg^{-1}$ groups. Three minutes prior to surgical initiation, oliceridine was administered intravenously, followed by propofol (Fresenius Kabi Austria GmbH, Hafnerstraße 36, A-8055 Graz, Austria) at a bolus dose of 2 mg $kg^{-1}$ infused over 30–60 seconds

and maintained at 6 mg $kg^{-1}$ $h^{-1}$. Cervical dilation was initiated by the surgeon upon confirmed loss of consciousness (defined as absence of eyelash reflex and the modified observer's assessment of alertness/sedation (MOAA/S) score <2). When cervical dilation reached 1 cm in diameter, a 27-Fr (9 mm) outer sheath hysteroscope was inserted. Success was defined as no body movement response during cervical dilation. Failure was defined as any body movement during cervical dilation. If patients did not achieve adequate analgesia (MOAA/S >1, involuntary movement, or heart rate (HR) increase > 20 beats $min^{-1}$) after the initial doses of oliceridine and propofol, supplemental doses of propofol (0.5 mg $kg^{-1}$ each time) were administered at intervals exceeding 1 minute. All anesthetic agents were discontinued at the end of the hysteroscopic procedure. After the surgery, the patient was transferred to the postanesthetic care unit (PACU) for a 30-minute observation and was returned to the ward upon meeting the required standards.[14] Postoperative pain intensity was assessed using a visual analogue scale (VAS; 0–10 points, with 0 = no pain and 10 =the most severe pain). Intravenous sufentanil (5 μg) was administered if VAS scores >3. The MOAA/S scale, ranging from 5 (fully alert) to 0 (unresponsive to noxious stimuli), was used to describe deep sedation states and is widely employed in anesthesia research.[15,16] Injection pain was defined as verbally reported pain immediately following initial propofol administration.

Adverse hemodynamic events were defined as bradycardia (heart rate <50 beats per minute) and hypotension (systolic blood pressure <90 mmHg or <80% of baseline), treated with intravenous atropine 0.5 mg and norepinephrine 4 μg, respectively. Hypoxia was defined as $SpO_2$ <90%, managed by lifting the chin and/or providing pressure-assisted ventilation via a face mask. For patients experiencing nausea and vomiting, 4 mg of ondansetron was administered intravenously. Other adverse events, including nausea, vomiting, and arrhythmia, were also monitored.

## Observational Indicators

### Primary Outcome

Success rate in each dose group (0.01, 0.015, 0.02, 0.025, or 0.03 mg $kg^{-1}$ groups).

### Secondary Outcomes

Included total propofol dose, operative time (from cervical dilation initiation to hysteroscope removal), and anesthesia recovery time (defined as the interval from propofol discontinuation to patient awakening and eye opening). HR, systolic blood pressure (SBP), $SpO_2$, and MOAA/S were recorded at the following time points: before induction (T1), at the start of surgery (T2), during cervical dilation (T3), at the end of surgery (T4), and upon anesthesia recovery (T5). Postoperative pain intensity at 30 minutes (T6) was assessed using VAS score. Adverse events were also documented, including body movement reactions, hypotension (systolic blood pressure <90 mmHg or <80% of baseline), sinus bradycardia (HR <50 beats $min^{-1}$), hypoxia ($SpO_2$ <90%), dizziness,arrhythmia,nausea and vomiting.

## Sample Size Calculation and Statistical Analysis

The preliminary experimental results from patients undergoing hysteroscopy indicated that the estimated $ED_{50}$ and $ED_{90}$ of oliceridine were approximately 0.09 mg $kg^{-1}$ and 0.28 mg $kg^{-1}$, respectively. To adequately characterize the dose-response relationship, the lowest dose group was designed to be below the pilot $ED_{50}$ value, while the highest dose group exceeded the pilot $ED_{90}$ value. Accordingly, five dose groups of oliceridine were established: 0.01 mg $kg^{-1}$, 0.015 mg $kg^{-1}$, 0.02 mg $kg^{-1}$, 0.025 mg $kg^{-1}$, and 0.03 mg $kg^{-1}$. The corresponding success rates for these five groups in the preliminary experiment were 30%, 40%, 50%, 70%, and 90%, respectively. This study necessitated 11 patient samples per group to maintain a power of 0.90, with the significance level established at 0.05 (PASS11, NSCC, LCC, Kaysville, utilizing the Cochran-Armitage test for trend in proportions). Anticipating possible dropouts, we resolved to augment the sample size of each dosage group to 20 cases.

Statistical analysis was conducted utilizing SPSS version 25.0 (IBM Corp, Armonk, NY). The Shapiro–Wilk test was employed to evaluate the normality of the data. For data that adhered to a normal distribution, one-way analysis of variance (ANOVA) was implemented, succeeded by the least significant difference (LSD) post hoc test for conducting pairwise comparisons to ascertain significant differences within or between groups. The Kruskal–Wallis test was utilized for data that did not conform to a normal distribution, followed by the Dunn-Bonferroni post hoc test. Categorical data

were subjected to analysis via the chi-square test or Fisher's exact test.P values < 0.05 were deemed to be statistically significant.

Probit regression was employed to examine the dose-effect relationship. This statistical method estimated the doses of oliceridine necessary to attain the anticipated clinical effects, specifically the probabilities of $ED_{50}$ and $ED_{90}$, when administered in conjunction with propofol. Confidence intervals (CIs) for $ED_{50}$ and $ED_{90}$ were computed to ascertain the precision and dependability of these estimations. P values < 0.05 were deemed to be statistically significant.

## Results

The study included a total of 122 female participants, of whom 22 were excluded (Figure 1). The demographic characteristics of the patients are presented in Table 1. Statistical analysis revealed no significant differences among the groups in terms of age, height, weight, BMI, history of non-vaginal delivery, or operative duration (P > 0.05) (Table 1).

The dose-response relationship of oliceridine with propofol for day-case hysteroscopy were performed using probit regression. The probit regression curve is shown in Figure 2. The estimated values of $ED_{50}$ and $ED_{90}$ with 95% CIs for intravenous oliceridine combined with propofol in hysteroscopy were 0.01 (0.004 to 0.013) mg $kg^{-1}$ and 0.025 (0.020 to 0.050) mg $kg^{-1}$, respectively.

According to our definition, the 0.01, 0.015, 0.02, 0.025, and 0.03 mg $kg^{-1}$ groups had 10, 16, 15, 18, and 19 successful cases respectively (20 cases per group). The success rates of oliceridine without body movement response during cervical dilation were 50%, 80%, 75%, 90%, and 95% respectively (Table 2). There were no differences in propofol requirement, anesthesia recovery time, or VAS at 30 minutes postoperation among the groups. The incidences of adverse reactions such as hypotension, respiratory depression, nausea and vomiting, postoperative dizziness, and arrhythmia showed no statistically significant differences. Propofol injection pain was significantly lower in patients given 0.02, 0.025, and 0.03 mg $kg^{-1}$ oliceridine (45%, 40%, and 30%, respectively) than those given 0.01 mg $kg^{-1}$ (80%)

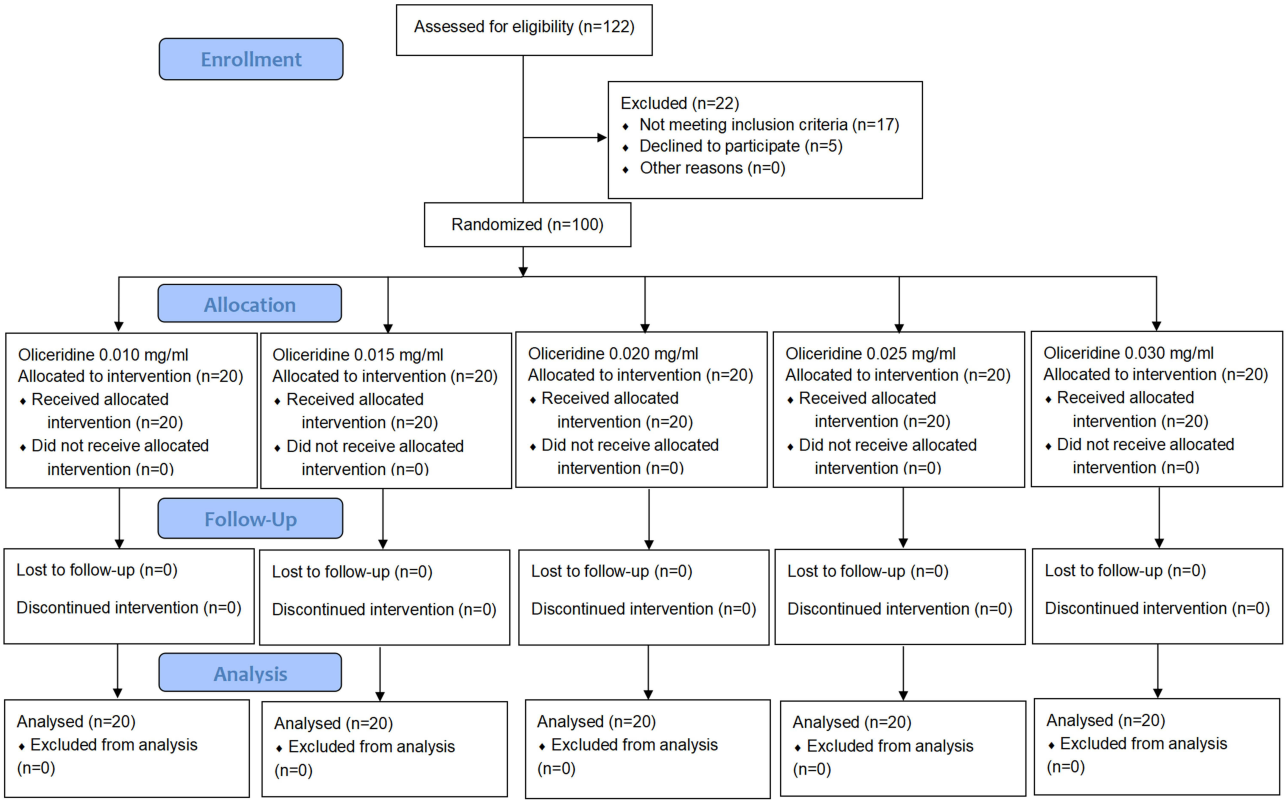


**Figure 1** CONSORT showing flow of patients.

**Table 1** Demographic Data

| | Oliceridine 0.010 mg kg$^{-1}$ (n = 20) | Oliceridine 0.015 mg kg$^{-1}$ (n = 20) | Oliceridine 0.020 mg kg$^{-1}$ (n = 20) | Oliceridine 0.025 mg kg$^{-1}$ (n = 20) | Oliceridine 0.030 mg kg$^{-1}$ (n = 20) | *P* value |
|---|---|---|---|---|---|---|
| Age (y) | 42.6 ± 7.4 | 38.0 ± 8.8 | 41.5 ± 7.5 | 39.2 ± 7.6 | 39.1 ± 7.8 | 0.320 |
| Height (cm) | 160.9 ± 4.9 | 159.2 ±4.6 | 161.3 ± 5.7 | 160.6 ± 4.1 | 161.9 ± 4.3 | 0.481 |
| Weight (kg) | 56.0 ± 7.2 | 58.5 ± 6.3 | 56.0 ± 6.6 | 58.2 ± 7.3 | 57.1 ± 4.5 | 0.608 |
| BMI (kg m$^{-2}$) | 21.6 ± 2.1 | 23.0 ± 1.5 | 21.5 ± 2.4 | 22.3 ± 2.1 | 21.8 ± 1.6 | 0.094 |
| History of non-vaginal delivery | 8 (40%) | 9 (45%) | 7 (35%) | 7 (35%) | 7 (35%) | 0.955 |
| Surgery duration (min) | 17.3 ± 6.8 | 20.3 ± 9.5 | 18.3 ± 6.7 | 18.3 ± 6.2 | 17.9 ± 7.0 | 0.752 |

**Notes**: Data are mean ± SD (standard deviation) or number (%).

or 0.015 mg kg$^{-1}$ (80%) ($P < 0.05$ for both). The difference among dose groups was statistically significant ($P = 0.001$) (Table 3).

## Discussion

This investigation assessed the effectiveness of various doses of oliceridine in conjunction with propofol for day-case hysteroscopy. By analyzing analgesic efficacy, hemodynamic alterations, and the prevalence of adverse events, the $ED_{90}$ value for oliceridine in combination with propofol for intravenous analgesia during hysteroscopy was established at 0.025 mg kg$^{-1}$. The findings indicated that the administration of oliceridine at the $ED_{90}$ dose alongside propofol for intravenous anesthesia yielded favorable anesthetic outcomes. Notably, to date, no studies has been conducted to specifically ascertain the $ED_{90}$ value for oliceridine in conjunction with propofol for anesthesia during hysteroscopy.

Due to its excellent sedative properties, rapid onset, and short duration of action, propofol is particularly suitable for anesthesia in day-care hysteroscopy. A meta-analysis on propofol for sedation during colonoscopy demonstrated that propofol enhanced the sedative effect but did not significantly alter the analgesic efficacy of opioids.[17] However, propofol may exert time- and dose-dependent inhibitory effects on the cardiovascular and respiratory systems, while traditional opioids also carry the adverse effect of opioid-induced respiratory depression (OIRD),[18–20] potentially the most severe ORAE. The combination of these agents might further exacerbate respiratory depression, posing potentially fatal

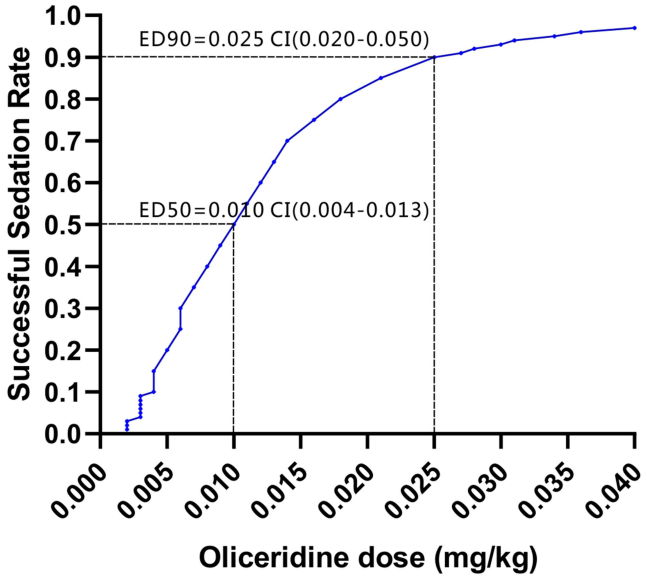


**Figure 2** Dose–response curve of oliceridine for day-case hysteroscopy.


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**Table 2** Observed Proportion of Patients with Successful Anesthesia at Different Doses of Oliceridine

| Oliceridine (mg $kg^{-1}$) | Success | Number of Patients | Successful Anesthesia Rate (%) |
|---|---|---|---|
| 0.010 | 10 | 20 | 50 |
| 0.015 | 16 | 20 | 80 |
| 0.020 | 15 | 20 | 75 |
| 0.025 | 18 | 20 | 90 |
| 0.030 | 19 | 20 | 95 |

**Table 3** Postoperative Data and Side Effects

| | Oliceridine 0.010 mg $kg^{-1}$ (n = 20) | Oliceridine 0.015 mg $kg^{-1}$ (n = 20) | Oliceridine 0.020 mg $kg^{-1}$ (n = 20) | Oliceridine 0.025 mg $kg^{-1}$ (n = 20) | Oliceridine 0.030 mg $kg^{-1}$ (n = 20) | *P* Value |
|---|---|---|---|---|---|---|
| Propofol requirements (mg $min^{-1}$) | 14.1 ± 3.4 | 13.5 ± 4.1 | 13.3 ± 3.5 | 13.6 ± 3.4 | 13.3 ± 3.1 | 0.941 |
| Time to anesthesia emergence (min) | 10.0 (8.3–10.8) | 11.0 (9.3–11.8) | 10.0 (9.0–11.8) | 10.0 (8.3–12.0) | 10.5 (9.0–12.8) | 0.378 |
| Injection pain | 16 (80%)# | 16 (80%)& | 9 (45%) | 8 (40%) | 6 (30%) | 0.001 |
| VAS at 30 minutes postoperation | 0 (0–4) | 1 (0–1) | 0 (0–1) | 1 (0–2) | 0 (0–2) | 0.273 |
| Hypotension | 2 (10%) | 2 (10%) | 4 (20%) | 2 (10%) | 5 (25%) | 0.540 |
| Respiratory Depression | 4 (20%) | 4 (20%) | 6 (30%) | 5 (25%) | 4 (20%) | 0.925 |
| Nausea and Vomiting | 2 (10%) | 0 (0%) | 1 (5%) | 0 (0%) | 0 (0%) | 0.245 |
| Postoperative Dizziness | 1 (5%) | 3 (15%) | 0 (0%) | 1 (5%) | 1 (5%) | 0.378 |
| Arrhythmia | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) | > 0.999 |

**Notes**: Data are mean ± SD (standard deviation), median (interquartile range) or number (%).#P < 0.05 for comparison with one of the other three groups (Oliceridine 0.020, 0.025 and 0.030 mg $kg^{-1}$) after Bonferroni correction. &P < 0.05 for comparison with one of the other three groups (Oliceridine 0.020, 0.025 and 0.030 mg $kg^{-1}$) after Bonferroni correction.
**Abbreviation**: VAS, visual analogue scale.

consequences. Oliceridine, being the inaugural and exclusive biased μ-opioid receptor agonist, selectively activates the G-protein pathway (mediating analgesia) while avoiding activation of the β-arrestin pathway (associated with opioid-related adverse effects),[21] thereby mitigating drug-related adverse reactions. In the APOLLO-2 trial (a Phase III study for treating acute postoperative pain after abdominoplasty), oliceridine showed dose-dependent increases in respiratory safety burden representing cumulative duration of respiratory safety events), but exhibited significantly lower incidence of respiratory depression compared to morphine.[8]

Our study revealed that the incidence rates of respiratory depression across the five oliceridine dose groups were 20%, 20%, 30%, 25%, and 20%, respectively, which may be associated with the administration of nasal oxygen supplementation to patients, albeit without any statistically significant disparities. This implies that within the investigated dosage spectrum, oliceridine does not manifest dose-proportional respiratory depression. Notably, discrepancies exist when compared with the APOLLO-2 trial results, which may be attributed to: (1) Different study methodologies - APOLLO-2 employed postoperative PCA administration while this study used intraoperative single-dose administration; (2) Surgical type variations - different procedures involve significantly varying operation durations and pain intensities that may influence outcomes. Furthermore, our observations demonstrated that desaturation episodes were readily resolved through chin-lift maneuvers without requiring mask ventilation support, indicating that the combination of oliceridine and propofol did not significantly increase respiratory depression risk. All affected patients maintained adequate oxygenation through simple interventions, underscoring the clinical safety profile of this drug combination.

Nausea and vomiting represent major postoperative concerns, with 37% of ambulatory surgery patients experiencing post-discharge symptoms,[22] while also being among the most common ORAEs of opioids.[23–26] Phase III clinical trials of oliceridine consistently showed significantly lower frequency or severity of nausea and vomiting. This aligns with our

findings where nausea/vomiting incidence ranged 0–10% across groups without statistical significance, confirming oliceridine's favorable gastrointestinal safety profile.

Propofol injection pain is a frequent patient complaint during anesthesia, occurring in 28–90% of cases and sometimes being severe.[27,28] It is commonly believed that propofol activates the kallikrein-kinin system, triggering the release of bradykinin. This response causes venous dilation and heightened permeability, which increases contact between the aqueous component of propofol and free nerve endings, thereby producing pain. A meta-analysis conducted by Elham et al showed that opioids were one of the most effective intervention.[29] This study found that 0.02 to 0.03 mg $kg^{-1}$ of oliceridine significantly reduced propofol injection pain, while the incidence remained high at doses of 0.015 mg $kg^{-1}$ and below. This suggests that oliceridine has a significant effect on alleviating propofol injection pain at higher doses, and its efficacy is positively correlated with the dose. This finding holds important implications for improving patients' surgical experience and satisfaction. Future research could further explore the application of oliceridine in combination with other drugs for propofol injection pain management, aiming to provide patients with safer and more effective analgesic solutions.

While previous reports noted significant hypotension with propofol alone,[19] our data showed lowest hypotension incidence in 0.01mg $kg^{-1}$ and 0.015mg $kg^{-1}$ groups and highest in 0.03mg $kg^{-1}$ group. Although statistical significance was not reached, this trend suggests a potential synergistic interaction between oliceridine and propofol on propofol-induced hypotension. No arrhythmias occurred across groups, further supporting oliceridine's safety and feasibility in this combination regimen. Additionally, we observed no significant prolongation of recovery time with increasing oliceridine doses, low postoperative dizziness incidence, and absence of moderate-to-severe pain in all groups except one case of moderate pain in the 0.01mg $kg^{-1}$ group. Though these adverse events showed no intergroup statistical differences, larger clinical studies are needed for confirmation. Overall, these findings provide additional clinical evidence supporting oliceridine's application in hysteroscopic anesthesia.

Our study confirmed the efficacy and safety of oliceridine combined with propofol for sedation in day-case hysteroscopy.However, there are also several limitations. First, our research only included relatively healthy female patients (ASA I or II), excluding elderly, obese, or other medically compromised patients (ASA III or IV). Oliceridine's efficacy, safety, and dose-response relationships in these special populations remain unclear and require comparative investigation. Second, with propofol fixed at 2 mg $kg^{-1}$, we did not examine whether oliceridine co-administration could reduce propofol requirements. Future studies should systematically evaluate pharmacodynamic interactions between variable propofol and oliceridine regimens to identify optimal dosing thresholds that maximize clinical efficacy while minimizing adverse effects. Third, in some studies, anesthesia depth monitoring was used to obtain more accurate propofol dosage.[30,31] In our study, the absence of depth of anesthesia monitoring resulted in a lack of precise guidance for sedation depth assessment. Finally, our study lacked post-discharge follow-up data, whereas some adverse events like PONV may persist or emerge after discharge,[22] necessitating further observation to evaluate long-term outcomes of this anesthetic regimen.

## Conclusion

In summary, our study revealed the dose–response relationships between oliceridine and propofol, with the $ED_{90}$ of oliceridine being 0.025 mg $kg^{-1}$ (95% CI: 0.020 to 0.050). It is recommended to use oliceridine for ASA I–II patients during day-case hysteroscopy due to its good analgesic effect, minimal impact on cardiovascular and respiratory depression, and low incidence of nausea and vomiting.

## Abbreviations

ASA, American Society of Anesthesiologists; BMI, body mass index; CIs, confidence intervals; CONSORT, Consolidated Standards of Reporting Trials; $ED_{90}$, 90% effective dose; $ED_{50}$, median effective dose; FDA, the United States Food and Drug Administration; HR, heart rate; NIBP, non-invasive blood pressure; $SpO_2$, pulse oxygen saturation; SBP, systolic blood pressure; MOAA/S, modified observer's assessment of alertness/sedation; SD, standard deviation; VAS, visual analog scores; ANOVA, analysis of variance; LSD, least significant difference; OIRD, opioid-induced respiratory depression; ORAE, opioid-related adverse event.

## Data Sharing Statement

Deidentified individual participant data will be provided. The data supporting this study are available from the corresponding author (Jing Yu, yujing985@163.com) upon reasonable request.

## Ethics Approval and Consent to Participate

This study was approved by the Research Ethics Committee of Zhejiang Xiaoshan Hospital and registered in the Chinese Clinical Trial Registry. All patients provided written informed consent prior to surgery. Our study complies with the Declaration of Helsinki.

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## Disclosure

The authors report no conflicts of interest in this work.

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