Journal of Pain Research

Dovepress
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ORIGINAL RESEARCH

Determining the Effective Dose of Oliceridine Compounded with Propofol for Painless Hysteroscopy: A Prospective Modified Dixon Sequential Dose-Finding Study

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Background: Oliceridine combined with propofol is suitable for intravenous anesthesia in painless hysteroscopy. This study aimed to determine the 50% effective dose (ED_{50}) and 95% effective dose (ED_{95}) of oliceridine compounded with propofol for painless hysteroscopy.

Methods: In all, 29 patients aged 18–60 years who were scheduled for painless hysteroscopy under intravenous anesthesia were recruited, and a total of 26 patients were enrolled in the final analysis. The trial was conducted using the modified Dixon sequential method, with an initial dose of 1.5 mg of oliceridine, followed by 2.0–2.5 mg/kg of propofol administered 1 minute later. Whether the dose of oliceridine was increased or decreased depends on the prior operation. If the hysteroscopy failed (positive response), which was defined as inadequate cervical dilatation, patient body movements, frowning, heart rate (HR), or mean arterial pressure (MAP) greater than 20% of the baseline value, or a MOAA/S score ≥ 2, the subsequent dosage of oliceridine was increased by 0.1 mg. Conversely, the dose was decreased by 0.1 mg. At least seven crossover waves had to occur before the formal test was stopped. The probit regression method was used to determine the ED_{50} and ED_{95} with 95% confidence intervals (CIs).

Results: The ED_{50} and ED_{95} of oliceridine in patients were 1.583 (95% CIs: 1.444–1.857) mg and 1.848 (95% CIs: 1.701–4.409) mg, respectively.

Conclusion: A dose of 1.848 mg oliceridine compounded with propofol provides an effective anesthesia approach for painless hysteroscopy. Future larger, multicenter studies will help to expand the population range of oliceridine use and explore its potential benefits and risks.

Keywords: ED_{50}, ED_{95}, oliceridine, painless hysteroscopy

Introduction

Hysteroscopy has gained widespread application in gynecological procedures, while surgical operations such as cervical dilatation and uterine distension are strongly stimulated, frequently causing patients considerable discomfort and even making it difficult for the gynecologist to operate due to the patient's struggle and twisting movements.[1–3] Previous research has indicated that severe pain and discomfort in women was a potential risk within hysteroscopy.[4] With the proposal and development of the concept of enhanced recovery after surgery (ERAS), painless hysteroscopy has become a crucial choice for gynecological diagnosis and treatment based on its advantages of safety and tolerance. Propofol combined with opioids is a commonly used sedation and analgesia scheme at present, which can inhibit the severe pain caused by cervical dilatation and provide a satisfactory anesthetic effect for hysteroscopy.[5,6]

Received: 20 August 2025
Accepted: 10 December 2025
Published: 18 December 2025

However, the incidence of respiratory and circulatory depression in classical opioids during operation is high, so it is necessary to further explore an anesthesia scheme that is more suitable for hysteroscopy.

As a selective G protein signal transduction pathway, oliceridine is an opioid receptor agonist with low effect on β inhibitory protein recruitment, with rapid onset and short half-life.[7,8] According to its unique partial ligand mechanism, it can effectively relieve pain and reduce adverse reactions such as respiratory depression, nausea and vomiting.[8–10] The pharmacodynamic characteristics of rapid onset and short-acting duration of oliceridine make it more suitable for situations where procedural sedation and recovery are needed than classical opioids. Although current research and studies have highlighted the potential of oliceridine in the field of sedation and analgesia,[9–11] the optimal effective dose of oliceridine for painless hysteroscopy and its safety and efficacy remain to be determined. In order to determine the 50% effective dose (ED_{50}) and 95% effective dose (ED_{95}) of oliceridine combined with propofol during painless hysteroscopy, we designed this prospective dose-finding study so as to provide a reference for future clinical application.

Methods

Study Design

This prospective dose-finding study was conducted from March 2025 to June 2025 at the Zigong Maternal and Child Health Care Hospital and was approved by the ethical committee (2024-IRB-017). The protocol was registered with the Chinese Clinical Trials Registry on 17 March 2025 (ChiCTR2500098967), and all experiments were conducted following the principles of the Helsinki Declaration and the CONSORT guidelines. Informed consent forms were signed by all participants before enrollment in this study.

Patients

Patients who were scheduled for painless hysteroscopy under intravenous anesthesia in our hospital were recruited. Inclusion criteria: (1) age of 18–60 years; (2) BMI index of 18–25 kg/m^2; (3) American Society of Anesthesiologists (ASA) physical status of I–II. Exclusion criteria were as follows: (1) Patients who refuse to participate in this trial; (2) Patients with hypertension or other abnormal functions such as heart, lung, liver, and kidney; (3) Patients with obstructive sleep apnea syndrome or difficult airways; (4) Patients with respiratory infections in the recent 2 weeks; (5) Patients with psychiatric diseases or long-term history of taking sedative and analgesic drugs; (6) Those who were allergic to general anesthesia drugs.

Anesthesia Protocol

Before surgery, all patients were required to fast for at least 8h and had imbibed no clear liquids for 2h before intravenous anesthesia. Routine monitoring, including electrocardiogram (ECG), blood pressure (BP), and pulse oxygen saturation (SpO_2), was performed as soon as the patient entered the operation room, and oxygen was delivered at 5 L/min with a mask. After the peripheral venous channel was established in the left hand, anesthesia induction was started by the same anesthesiologist according to the experimental scheme. The initial dose of oliceridine was determined to be 1.5 mg based on the previous published research,[7,9] and followed by 2.0–2.5 mg/kg of propofol at a constant speed for more than 30s, and then pumped intravenously at 2.0 mg/kg/h. After the patient lost consciousness and the modified observer's assessment of alertness and sedation (MOAA/S) score achieved 0 points, the hysteroscopy was performed by a skilled gynecologist.

The modified Dixon sequential method is recognized as one of the simple and efficient approaches for the determination of the effective dose of drugs and therefore was used to conduct this study.[12,13] The next sequential oliceridine dose depended on whether prior hysteroscopy had failed, which was defined as inadequate cervical dilatation and patient body movement, frowning, heart rate (HR) or mean arterial pressure (MAP) greater than 20% of the baseline value, or a MOAA/S score ≥ 2.[5,14] If the operation failed (positive response), the subsequent dose of oliceridine was adjusted up by 0.1 mg. Conversely, the dose was adjusted down by 0.1 mg if the examination was successful (negative response). The formal trial starts with the first crossover wave and stops after seven crossovers

are observed. Patients were divided into the positive group or the negative group according to their response during hysteroscopy.

An additional 0.5–1.0 mg/kg propofol was added when there was an occurrence of a positive reaction during the operation and then continued after the anesthesia was satisfactory. The vital signs and respiratory status of patients were closely monitored. If the SpO_2 drops below 90%, lift the mandible to open the airway first and provide oxygen assistance. Ephedrine (6 mg) was given to raise BP when MAP is below 60 mmHg or basic BP is lower than 20%. Atropine (0.5 mg) was used to treat bradycardia (HR<50) if needed.

The MOAA/S score was chosen to evaluate the sedation scale of patients:[14] sensitive to name calls in a normal tone is 5 points; unresponsive to name calls in a normal tone is 4 points; only responsive to loud or repeated name calls is 3 points; responsive to slight stimulation or shaking is 2 points; responsive to painful stimulation is 1 point and have no response is 0 point.

Observation Indicators

The primary outcome was the 50% effective dose (ED_{50}) and 95% effective dose (ED_{95}) of oliceridine compounded with propofol for hysteroscopy. The secondary outcome included the vital signs and visual analog scale (VAS) scores at different time points, consumption of drugs, surgical duration, recovery time, and adverse events. The vital signs (HR, SpO_2, MAP, and RR) were measured before analgesia (T_0), after injection of propofol (T_1), and at the moment of cervix dilation (T_2). Pain evaluation using the VAS scores at postoperative 2h, 6h, and 24h. The incidence of adverse events such as nausea and vomiting, dizziness, respiratory depression, and hypotension during the 24 h postoperatively was calculated.

Statistical Analysis

All of the individual participant data were analyzed using SPSSAU (https://spssau.com/indexs.html) and GraphPad Prism version 9.0.0. The normally distributed data were expressed by the mean ± SD, and compared across groups by using the independent samples students' *t*-test. Repeated measurement data were analyzed using repeated measures ANOVA. The non-normal distributed data were expressed by the median (interquartile range), and comparison between groups was conducted using the Mann–Whitney *U*-test. The categorical variables were expressed as percentages and compared using the Chi-square test or Fisher's exact probability method, where appropriate. The ED_{50} and ED_{95} values of oliceridine combined with propofol and their 95% confidence interval were determined utilizing Probit analysis via probability unit regression. The *p*-value was set lower than 0.05, indicating that the difference is statistically significant.

Results

A total of 29 eligible patients were recruited for this study, and 3 patients were excluded. Consequently, 26 patients were included in the final analysis (Figure 1). The baseline demographic characteristics are presented in Table 1, such as age, height, weight, BMI, and ASA classification, and they were similar among the two groups ($p>0.05$). Table 2 summarizes the perioperative information of the patients, and there was no significant difference in surgical duration, time of recovery, or initial dose of propofol, except for the total propofol dose and oliceridine dose. We recorded the VAS scores at 2 h, 6 h, and 24 h postoperative, and the comparative analysis indicated that VAS scores at 2 and 6 h after surgery of patients in the negative group were significantly lower than those in the positive group ($p<0.05$) (Table 2). Only one patient suffered from hypotension, and one patient had nausea and vomiting during the postoperative period. No significant differences were observed in the adverse events among the positive and negative groups ($p>0.05$) (Table 3).

The sequential dose of oliceridine combined with propofol for painless hysteroscopy is presented in Figure 2. The probit regression analysis yielded the equation probit (P)= −9.805 + 6.195 × oliceridine dose. The Pearson goodness-of-fit test χ^2 =5.164 (p=0.160) confirmed that the equation fully fitted the data. According to the modified Dixon

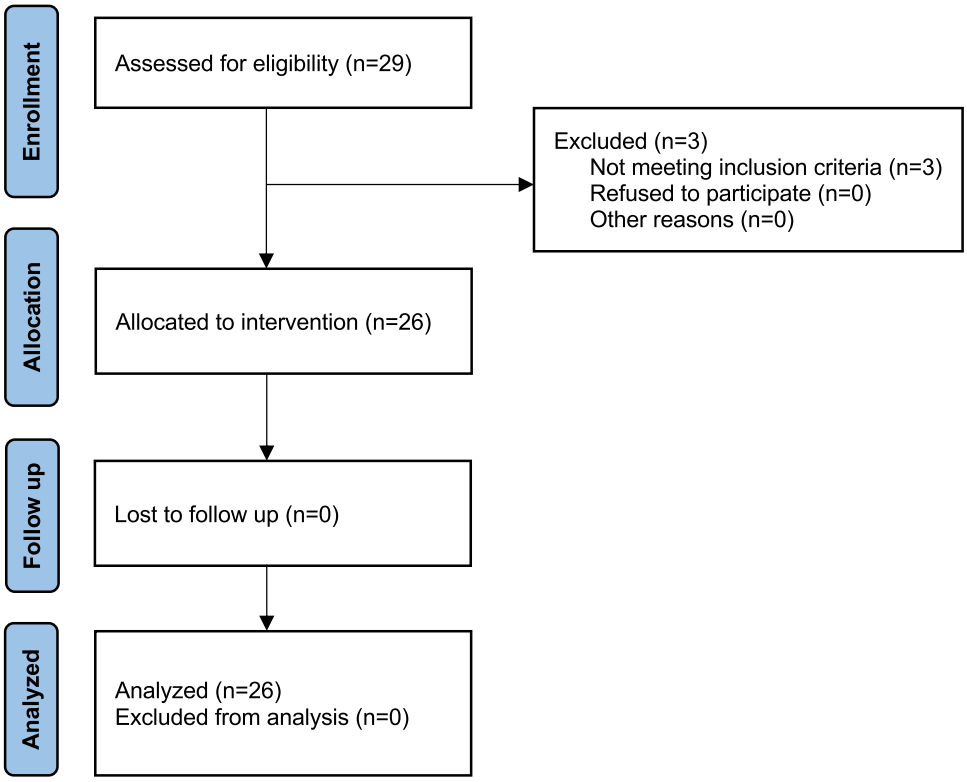

Figure 1 Flow chart of this study.

sequential method, the values of ED_{50} and ED_{95} were 1.583 (1.444–1.857) mg and 1.848 (1.701–4.409) mg, respectively.

The results of hemodynamic and respiratory parameters at T_0, T_1, and T_2 are shown in Table 4. Compared to T_0, the MAP and RR at both T_1 and T_2 were considerably lower ($p<0.05$).

Table 1 Demographic Characteristics

	Positive (n=14)	Negative (n=12)	*p*-value
Age (years)	34.29±9.10	34.08±8.37	0.954
Height (cm)	157.79±4.19	157.58±5.71	0.918
Weight (kg)	54.79±5.60	52.08±6.54	0.267
BMI (kg/m^2)	22.01±2.14	20.96±2.25	0.235
ASA (I/II cases)	6/8	5/7	0.951

Abbreviations: BMI, body mass index; ASA, America Society of Anesthesiologists.

Table 2 Comparison of the Perioperative Information of the Patients

	Positive (n=14)	Negative (n=12)	*p*-value
Surgical duration (min)	21.0±14.90	18.67±8.62	0.637
Time of recovery (min)	2.21±1.53	1.42±0.67	0.094
Oliceridine dose (mg)	1.52±0.09	1.62±0.10	0.023*
Initial dose of propofol (mg)	131.79±19.28	122.08±17.25	0.192
Total dose of propofol (mg)	244.14±90.72	161.42±50.64	0.010*
VAS score at 2h after surgery	2[0, 3]	0[0, 1]	0.009*
VAS score at 6h after surgery	1[0, 1.25]	0[0, 0]	0.047*
VAS score at 24h after surgery	0[0, 0]	0[0, 0]	>0.999

Notes: *$p<0.05$.
Abbreviation: VAS, Visual Analgesia Scale.

Table 3 Incidence of Adverse Events Within 24 h Postoperatively

	Positive (n=14)	Negative (n=12)	*p*-value
Nausea and vomiting (n)	1 (7.11%)	0	>0.999
Respiratory depression (n)	0	0	-
Dizziness (n)	0	0	-
Hypotension (n)	0	1 (8.33%)	0.462

Discussion

Hysteroscopy, as a gynecological procedure, is known to be the gold standard for inspection of uterine pathological conditions and abnormal uterine bleeding.[4,15] Although the procedure is thought to be low-pain and well-tolerated, it is reported that almost 25% of patients were experiencing intolerable or even severe pain.[16] The cervical length and flexion, intrauterine pressure, and preoperative anxiety are multiple factors related to the pain during hysteroscopy.[2,15,17,18] Therefore, a right and appropriate anesthesia scheme is crucial for guaranteeing a smooth hysteroscopy and quick recovery. Intravenous anesthesia based on propofol has been used in clinics for more than 30 years for its stable, clear-headed recovery and antiemetic characteristics.[19] When it is co-administered with opioids (such as alfentanil,[5] nalbuphine,[6] and sufentanil),[20] it can inhibit the pain caused by cervical dilatation and provide a satisfactory anesthetic effect for hysteroscopy. However, it is worth noting the risk of respiratory and cardiovascular suppression and gastrointestinal-related adverse events.

As the first G-protein biased μ opioid receptor agonist, Oliceridine selectively activates the G-protein signaling pathways and weakens the effect of β-arrestin recruitment. This partial ligand mechanism enables it to provide equal or even better analgesia while reducing the incidence of opioid-related adverse events.[7,21,22] Oliceridine provided comparable analgesia efficacy with superior safety compared to sufentanil in gastrointestinal endoscopy.[23] However, there are a few studies that have paid attention to oliceridine in painless hysteroscopy. Therefore, it is imperative to conduct this study to explore the effective dose of oliceridine in hysteroscopy and evaluate its safety.

Oliceridine offers a rapid onset of action that takes effect 1–3 min after administration, and the peak time is obviously faster than morphine (5 min vs 30 min).[7,24] Previous research recommended that the initial dose of oliceridine is 1.5 mg, with a maximum single dose not to exceed 3 mg due to safety concerns.[7,25,26] Hence, the initial dose of oliceridine in this study was set at 1.5 mg and was given 1 min before the injection of propofol. According to the modified Dixon sequential method, our prospective dose-finding study determined that the ED_{50} and ED_{95} values of oliceridine compounded with propofol for painless hysteroscopy were 1.583 (1.444–1.857) mg and 1.848 (1.701–4.409) mg, respectively.

Perioperative opioid use was associated with respiratory depression and postoperative nausea and vomiting (PONV), and this may prolong the hospital stays and cost of patients.[27,28] Recent studies have observed a higher incidence of opioid-induced respiratory depression (OIRD) and PONV in the sufentanil group during the hysteroscopy.[20,29] In this trial, only one patient experienced respiratory depression during the operation and promptly was relieved by mask

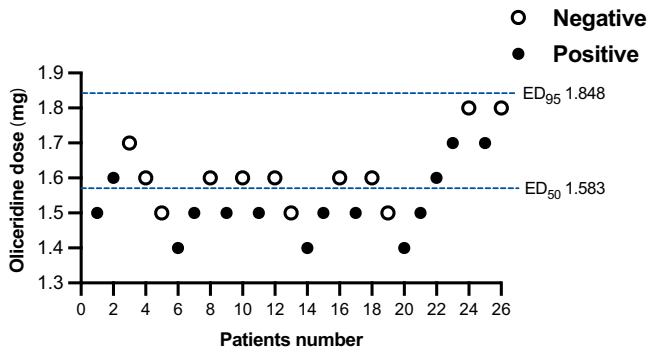

Figure 2 Sequence diagram of oliceridine for painless hysteroscopy. A circle indicates a negative response, while a filled circle represents a positive response.

https://doi.org/10.2147/JPR.S557764

Table 4 Hemodynamic and Respiratory Parameters at Different Time Points

	T_0	T_1	T_2
MAP (mmHg)	87.54±11.10	80.62±9.50[a]	82.00±11.36[a]
HR (bpm)	78.12±14.03	75.92±10.90	74.42±11.13
SpO_2 (%)	99.27±0.83	99.58±0.64	99.54±0.65
RR (breaths/min)	19.58±0.86	18.12±1.45[a]	18.35±1.44[a]

Notes: [a]$p<0.05$, compared to T_0.
Abbreviations: MAP, mean arterial pressure; HR, heart rate; SpO_2, pulse oxygen saturation; RR, respiratory rate. T_0, before analgesia; T_1, after injection of propofol; T_2, at the moment of cervix dilation.

ventilation, and one patient had nausea and vomiting within 24 h postoperatively. Our results demonstrated that oliceridine compounded with propofol was safe for painless hysteroscopy. The lower incidence of respiratory depression and gastrointestinal adverse events related to oliceridine may be associated with the decrease of β-arrestin recruitment.[21] Propofol has an inhibitory effect on the cardiovascular system, and a significant reduction of MAP was observed at T_1 (after propofol injection). Although the MAP and RR at the T_1 and T_2 time points differed significantly compared to T_0, their fluctuating values were still within the range of 20% of the baseline. No serious adverse events were reported with oliceridine at any dose during the intraoperative and postoperative periods in this study. Given the circulatory and respiratory stability, it may encourage anesthesiologists to prefer this combination of oliceridine and propofol in hysteroscopy.

Intravenous injection of propofol stimulates blood vessels to release inflammatory mediators such as histamine, causing injection pain and even becoming the most painful memory of patients before operation.[30] A previous study has found that oliceridine can effectively reduce injection pain related to propofol.[31] However, our research does not include a direct comparison, and future clinical practice could verify this conclusion. Except for one patient whose VAS scores exceeded 3 at 2 h after hysteroscopy, the other patients had VAS scores below 3, suggesting that oliceridine exhibited a potent analgesic efficacy. Furthermore, patients recovered quickly, and more than 80% of patients woke up within 2 min after surgery. Compared with previous studies on the application of nalbuphine,[6] sufentanil,[20] and esketamine[32] in hysteroscopy, oliceridine showed a shorter recovery time from anesthesia. This rapid recovery may be associated with its short elimination half-life, indicating a more accelerated metabolism that makes it difficult to accumulate[8]. The attributes of efficient analgesia and rapid recovery demonstrated by these results align with the core principles of ERAS, which support the appropriateness of oliceridine for application in hysteroscopy.

Overall, this study estimated the effective dose of oliceridine compounded with propofol for painless hysteroscopy, and our findings supported that oliceridine is a promising choice for anesthesia management in hysteroscopy. However, several limitations of this study should be acknowledged. Firstly, the estimated effective dose of oliceridine compounded with propofol in our study only applies to patients with ASA I–II classification. In terms of proving the safety and applicability of oliceridine in the population, it is essential to investigate the appropriate dose for the elderly (>60 years), patients with obesity (>25 kg/m^2), and other health disorders (ASA III–IV). Secondly, the highest dose of oliceridine in this study was 1.8 mg, and no serious adverse events were observed in any patients. Further research is needed to assess the intraoperative and postoperative safety associated with the effective dose of 1.848 mg. Thirdly, the modified Dixon sequential method was commonly used to determine the median and effective dose of drugs based on its simplicity and effectiveness, whereas a small sample size may introduce selection bias. Hence, a multicenter study with large samples is required to increase the generalizability of the results and comprehensively evaluate the safety and efficacy of oliceridine for hysteroscopy.

Conclusion

In summary, a single dose of oliceridine can effectively inhibit cervical dilatation pain while making rapid recovery from anesthesia in patients undergoing hysteroscopy, and the ED_{50} and ED_{95} of oliceridine compounded with propofol were

1.583 and 1.848 mg, respectively. These findings will provide a clinical reference for the appropriate anesthesia approach for painless hysteroscopy. Future larger, multicenter studies will help to expand the population range of oliceridine use and explore its potential benefits and risks.

Data Sharing Statement

The data supporting the conclusions of this study are not public but are available from the corresponding author upon reasonable request.

Ethics Approval and Consent to Participate

Our study was performed in accordance with the Helsinki Declaration and its later amendments. The ethics committee of Zigong Maternal and Child Health Care Hospital approved this study (2024-IRB-017), and all participants signed informed consent forms.

Acknowledgments

We express our gratitude to the patients in this study for their cooperation and contributions.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, acquisition of data, analysis, or in all these areas, and took part in drafting, revising, or critically reviewing the article. All authors have read the final manuscript and agreed to be accountable for all aspects of the work and then approved this version to be published.

Funding

This study was supported by the Bethune Charity Foundation (J202402E055-16).

Disclosure

The authors declare that they have no competing financial interests or personal relationships that could have appeared to influence the work reported in this article.

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