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ED_{50} of hydromorphone suppressing body movement in artificial abortion: A dose-finding study

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Abstract: The present study attempted to investigate the median effective dose (ED_{50}) of hydromorphone on suppressing of body movement in artificial abortion. A total of 23 female patients were assigned into the study using the up-and-down method. The usage amount of hydromorphone for each patient was decreased or increased by a gradient, depending on whether the anterior patient's body movement during the abortion procedure is positive or not. By using probit regression analysis, the ED_{50} of hydromorphone was 19.637 μg/kg for the suppression body movement in abortion. This result may provide a reference for the safety and rational use of the drug in clinic.

Keywords: Median effective dose, hydromorphone, abortion, comfort

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INTRODUCTION

The artificial abortion procedure itself takes approximately 5~7 minutes. However, the discomfort caused by the surgical manipulation may prevent patients from adequately participating, necessitating anesthesia in the majority of cases (Renner *et al*., 2010). Considering patients' usual preference for a prompt hospital discharge, rapid-onset and rapid-offset intravenous anesthesia without tracheal intubation is a safe and comfortable choice (Gokhale *et al*., 2016).

Propofol is an intravenous sedative agent that is highly utilized in outpatient examinations and surgeries due to its rapid onset and offset of action (Langley and Heel, 1988; Skues and Prys-Roberts, 1989), but it lacks analgesic properties. Anesthesia with propofol alone can result in loss of consciousness but body movement in patients undergoing artificial abortion, which increases the risks of uterine perforation. Increasing the dosage of propofol alone may address the issue of body movement, but it would also heighten adverse reactions related to cardiovascular and respiratory depression. The combination of low-dose analgesic medications not only effectively inhibits body movement during artificial abortion, reduces the propofol dosage, but also alleviates postoperative uterine contractions pain (Jakobsson *et al*., 1991).

Hydromorphone, as an opioid analgesic, exhibits potent analgesic effects with a rapid onset and moderate duration of action, making it suitable for short surgical procedures such as artificial abortion (Quigley, 2002). However, there has been no published report identifying the optimal dose of hydromorphone for use during artificial abortion. This study will investigate the use of propofol combined with hydromorphone for painless artificial abortion to assess the median effective dose (ED_{50}) of hydromorphone in inhibiting body movement during the procedure.

MATERIALS AND METHODS

General information

This clinical study was conducted after receiving approval No. YXYJ-2024-0006 from the Hospital Ethics Committee. A signed written informed consent document was obtained from each patient prior to participation. Patients were screened consecutively and were enrolled from April 2024 to July 2024.

Inclusion criteria

The patients performed elective artificial abortion at an early pregnancy (<14 weeks) ; aged 18 to 45 years; body mass index (BMI) between 18 and 28 kg/m^2; American Society of Anesthesiologists (ASA) physical status I or II.

Exclusion criteria

The patients refused to participate in the study; allergy to hydromorphone or propofol; severe liver/kidney/ cardiopulmonary dysfunction; chronic painful diseases; alcoholism; alteration of the surgical procedure; occurrence of severe adverse events during the procedure.

METHODS

The patients fasted from solids and liquids at least 8 hours before the operation. After entering the operating room, venous access was obtained at the dorsum of the left hand using an 18-gauge cannula and oxygen inhalation of 4 L/min through a nasal tube was applied. Blood pressure (BP), electrocardiogram (ECG) and pulse oximetry (SpO_2) were measured. No other drug was given before anesthesia induction.

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After the appropriate surgical position had been established, the patient received intravenous injection of hydromorphone at a rate of 1 mg/min. Immediately following the completion of the hydromorphone injection, propofol was injected intravenously at a rate of 10 ml/min at a dose of 2 mg/kg and propofol was mixed with 2% lidocaine at a dose of 0.4 mg/kg to alleviate injection pain. The procedure was performed by the same obstetrician-gynecologist when the patient's eyelash reflex disappeared. During the procedure, when the patient exhibited movement that disrupted the gynecologist's operation, we categorized this as a 'positive' response and accordingly, we increased the hydromorphone dosage for the subsequent patient. Conversely, when there was no such movement, it was categorized as a 'negative' response and we decreased the hydromorphone dosage for the next patient.

According to the previous relevant research and our pre-experiment (Chen *et al*., 2022), the initial dose of hydromorphone for the first patient was 20 μg/kg, with a dose gradient of 2 μg/kg. Upon positive response, an extra 0.5 mg/kg of propofol was given. If systolic BP fell >20% from baseline, 6-12 mg of ephedrine was administered as needed. If heart rate (HR) dropped to <50 bpm, 0.3-0.5 mg of atropine was injected as appropriate. In case of upper airway obstruction, the jaw was elevated for ventilation. If SpO2 ≤ 92%, oxygen delivery was increased and assisted mask ventilation was applied until SpO2 ≥ 95%. After seven "Positive/Negative" crossovers, the sample size was achieved using the modified up-and-down method. All patients were transferred to the post-anesthesia care unit following the procedure and stayed there for at least 30 min.

Outcome assessments

The primary outcome measure was the ED_{50} of hydromorphone. The secondary outcome measures included operating time, awakening time and the Visual Analog Scale (VAS) score for uterine contractions pain 10 minutes post-awakening. The VAS score ranges from 0 to 10, with 0 indicating no pain and 10 indicating unbearable pain. Adverse events consisted of hypotension (a 20% reduction in systolic blood pressure compared to baseline or <80 mmHg), bradycardia (HR < 50 beats/min) and hypoxemia (SpO2 < 90%).

STATISTICAL ANALYSIS

Probit regression in SPSS 25.0 (SPSS Inc., Chicago, IL, USA) was employed to calculate the ED_{50} and ED_{95} of hydromorphone for suppressing body movement during abortions, along with their respective 95% confidence intervals (CI). The data were presented as means ± standard deviations, median [interquartile ranges], or number of patients (n), depending on the distribution of the data. P values less than 0.05 were considered statistically significant.

RESULTS

ED_{50} of hydromorphone

The up-and-down sequences showing the doses and responses of patients are presented in fig. 1. The dose-effect curve of hydromorphone for suppressing body movement during induced abortions is shown in fig. 2. The ED_{50} and 95% CI of hydromorphone suppressing body movement in abortion were 19.637 (18.236 ～ 20.893) μg/kg, while the ED_{95} and 95% CI were 21.933 (20.753～ 29.416) μg/kg.

Patients information

Table 1 presents all patients' characteristics. The characteristics consist of ASA, age, height, weight, body mass index (BMI), duration of procedure, recovery time, VAS score for uterine contraction pain 10 minutes post-surgery.

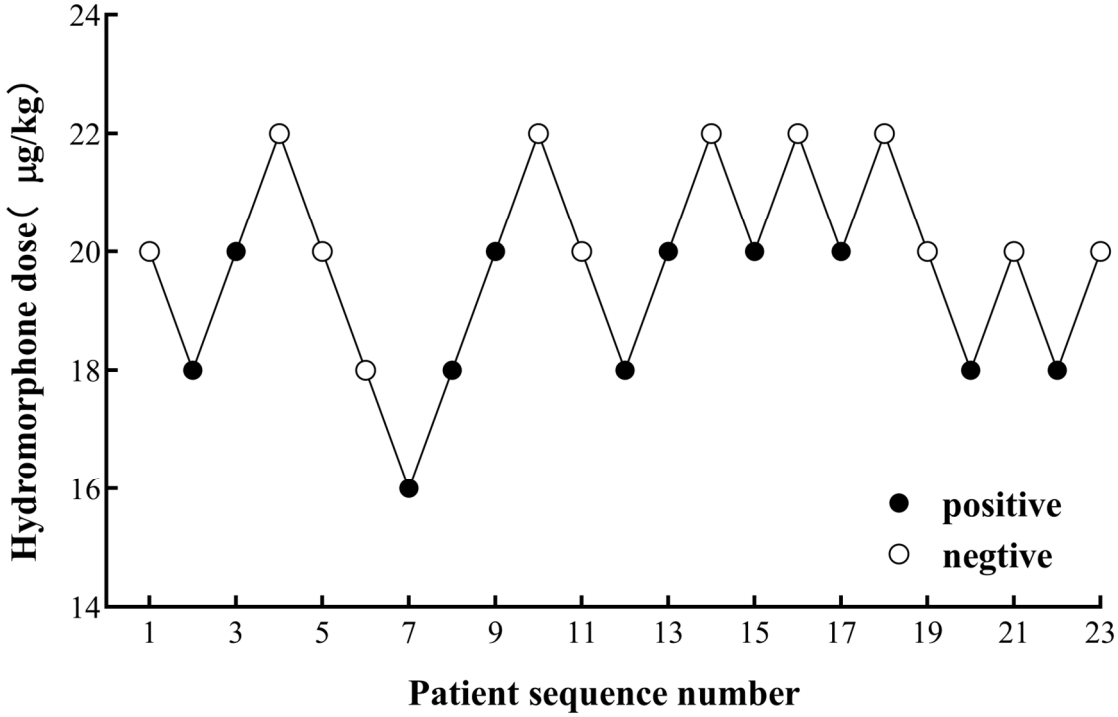
Anesthesia-related adverse events

Table 2 shows the perioperative adverse events. Of the 23 patients, two experienced mild injection-site pain, none suffered from hypoxemia, vomiting, or severe adverse events. Six patients encountered hypotension, five required a mandible lift for airway assistance and one had mild nausea. Additionally, during the injection of hydromorphone, four patients voluntarily reported severe dizziness, with one of them also experiencing palpitations.

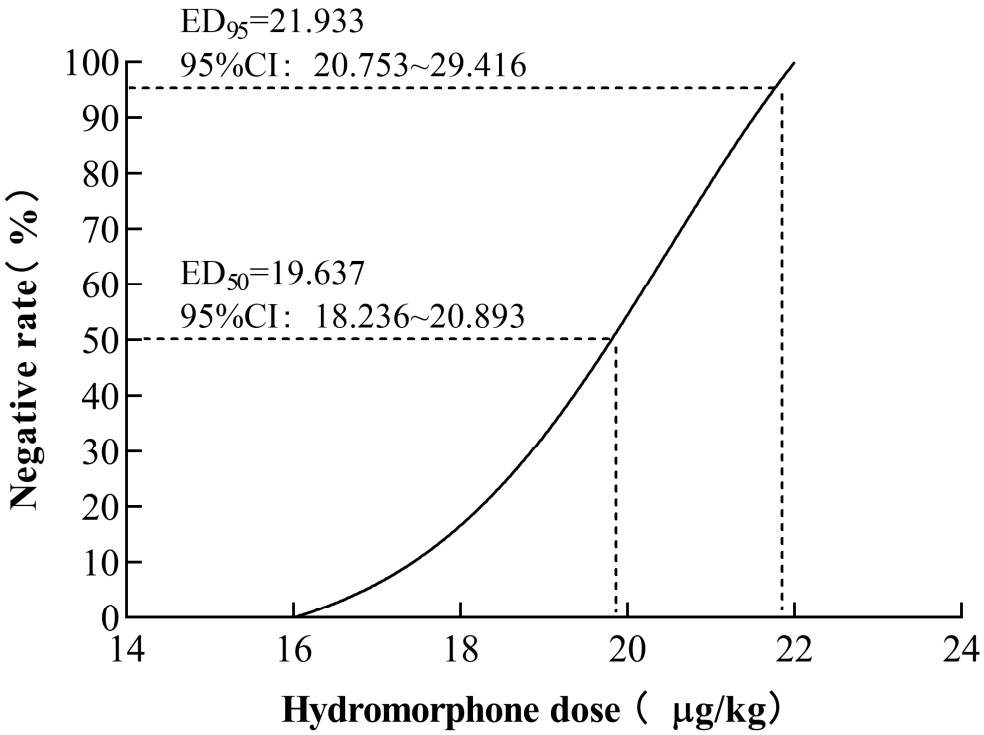
DISCUSSION

Propofol is a classic sedative in outpatient surgical anesthesia (Arellano *et al*., 2000; Joo and Perks, 2000), commonly used in conjunction with low-dose analgesic medications for intravenous anesthesia in outpatient settings (Zheng *et al*., 2023; Xie *et al*., 2017). This combination reduces the dose-related adverse reactions of single medication and provides some postoperative analgesic effects. The analgesic action of Hydromorphone typically onsets within 5 minutes, reaching a peak around 20 minutes, which helps to mitigate the post-abortion cramping pain and increase patient comfort. Our research findings indicate that the mean VAS score of 1.4 for pain level, which is considered mild, corroborates this aspect. Considering that the pain stimulation during abortion is greater than post-abortion, we decided to use the inhibition of body movement during abortion as the criterion to study the dose-effect relationship of Hydromorphone. Dixon's up-and-down method, which is renowned for its efficiency and reliability in determining the dose-effect relationship of drugs and widely applied in clinical drug efficacy research (Dixon, 1991; Lichtman, 1998), was selected as the investigational approach.

Pain with intravenous injection is a common side effect of propofol (Gajraj and Nathanson, 1996). The reported incidence of painful propofol injection in adults ranges as high as 28%～91% in the literature.



Note: The abscissa represented the patient sequence number, while the ordinate represented the hydromorphone dose (μg/kg).
Fig. 1: Dixon's up-down method plot.



Note: The abscissa represented the hydromorphone dose (μg/kg), while the ordinate represented the negative rate (%).
Fig. 2: A dose-response curve of hydromorphone suppressing body movement in abortion.

Table 1: Patients' characteristics.

Characteristic	n=23
ASA I/II (n)	22/1
Age (years)	32.7 ± 1.4
Height (cm)	162.3±1.1
Weight (kg)	57.1±1.7
BMI (kg/m^2)	21.6±0.5
Duration of procedure (min)	6.0(2.0)
Recovery time (min)	4.8±0.3
VAS score of uterine contraction pain	1.4±0.1

Table 2: Anesthesia-related adverse events.

Adverse events	Number of cases (percentage)
Hypotension	6 (26.1%)
Bradycardia	0
SpO2 < 90%	0
upper airway obstruction	5 (21.7%)
Injection-site pain	2 (8.7%)
Dizziness	4 (17.4%)
Mild nausea	1 (4.3%)
Palpitation	1 (4.3%)

To efficiently alleviate injection pain, our study mixed 0.2% lidocaine into the initial propofol injection (King *et al*., 1992; Scott *et al*., 1988). To minimize the potential side effects of lidocaine, a low dose was selected and the same proportion was added to each patient, thus balancing the possible anesthetic effect of lidocaine. Among the 23 patients, only two (8.7%) reported mild injection pain, significantly improving the comfort level of patients.

Six (26.1%) cases of hypotension occurred during the research process, all of which were a decrease in systolic blood pressure exceeding 20% of the baseline value, without systolic blood pressure values dropping below 80 mmHg. Hypotension is prone to occur during the induction of propofol and the inhibition of cardiovascular effects is one of the disadvantages of propofol (Goodchild and Serrao, 2015). Etomidate has an anesthetic effect similar to propofol but has a minimal impact on BP (Wu *et al*., 2013). However, the use of etomidate easily causes nausea and vomiting, reaching up to 30% (Holdcroft *et al*., 1976). The combination of propofol and etomidate can reduce the impact on the cardiovascular system, but we also need to consider the economic benefits for patients.

In addition, during the injection of hydromorphone, we recorded that four (17.4%) patients complained of severe dizziness, with one (4.3%) of the four reporting palpitations and nausea. Although the injection rate of hydromorphone was slow in our study, some side effects could not be avoided (Wermeling *et al*., 2010). Despite the patient who reported palpitations and nausea having stable vital signs throughout the procedure and no discomfort after awakening, patient comfort is a necessary consideration. In this study, administering propofol first to induce unconsciousness before injecting hydromorphone may be a strategy to address this issue (Ryu *et al*., 2008).

This study also has limitations. Firstly, the study population was limited to patients with a specific ASA classification and BMI and individuals who are weak, underweight, or obese have different physiological characteristics. Secondly, we did not fully consider whether the patients were first-time users of abortions or whether they were parous, which may also affect our research results.

CONCLUSION

In conclusion, under the conditions of this study, hydromorphone can be safely and effectively applied in abortions and the ED_{50} of hydromorphone was 19.637 μg /kg for the suppression of body movement in abortion when combined with propofol.

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Conflicts of interest

No conflicts of interest, financial or otherwise, are declared by the authors.

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