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CLINICAL TRIAL REPORT

Dixon Up-and-Down Method for Optimizing Oxycodone Dosage in Painless Colonoscopy

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Aim: Inadequate analgesia during painless colonoscopy can result in undesirable body movements, undermining patient safety and procedural success. Oxycodone, known for its dual κ- and μ-receptor agonism, may provide effective analgesia with a reduced incidence of adverse effects compared to other opioids. However, the optimal intravenous dose of oxycodone for suppressing body movement during colonoscopy has not been established.

Methods: This prospective, single-center, dose-finding study enrolled adult patients scheduled for painless colonoscopy. All participants received intravenous oxycodone in combination with propofol, with the oxycodone dose determined according to the Dixon and Massey up-and-down sequential allocation method. The primary outcome was the median effective dose (ED_{50}) of oxycodone required to suppress body movement during colonoscope insertion. Body movement was graded, and a positive response was defined as movement graded ≥2. The ED_{50} was estimated as the mean of crossover midpoints after at least seven reversal pairs, and the 95% confidence interval (CI) was determined by probit regression. Adverse events within 20 minutes after the procedure, including agitation, abdominal pain, nausea or vomiting, dizziness or headache, and postural instability, were also recorded.

Results: A total of 36 patients were enrolled. The calculated ED_{50} of oxycodone for suppression of body movement during colonoscope insertion was 0.055 mg/kg, 95% CI: 0.047–0.063 mg/kg.

Conclusion: Intravenous oxycodone, when dosed by the Dixon up-and-down method, is effective and safe for analgesia during painless colonoscopy.

Clinical Trial Registration: ChiCTR:ChiCTR2300077446.

Keywords: oxycodone, painless colonoscopy, up-and-down method, median effective dose, ED50, analgesia

Introduction

With the widespread adoption of the concept of comfort-focused medical care and rapid advances in endoscopic technology, painless gastrointestinal endoscopy has become a routine approach for the screening and treatment of gastrointestinal diseases.[1] In painless colonoscopic procedures, propofol is frequently used as the primary sedative due to its rapid onset and quick recovery profile.[2,3] However, achieving deep sedation with propofol alone—in order to meet the requirements of endoscopic manipulation—usually necessitates higher doses. This increases the risk of adverse effects, such as respiratory depression and hemodynamic instability, and may also prolong recovery time.[4,5] To overcome these limitations, the use of multimodal sedation strategies combining propofol with opioid analgesics has become common practice. This approach synergistically enhances the sedative effects of propofol, allows for a reduction in its dosage, and thus significantly improves hemodynamic stability, reduces the incidence of respiratory depression, and accelerates postoperative recovery and discharge.[6,7]

Currently, sufentanil is among the most widely used opioids for painless gastrointestinal endoscopy.[8] Nevertheless, sufentanil is associated with a relatively high incidence of postoperative nausea and vomiting (PONV) and may trigger

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coughing, both of which can compromise patient comfort and procedural safety.[9] Oxycodone, a potent opioid agonist with dual effects on κ and μ receptors, offers a unique pharmacological profile. It has a moderate onset time (approximately 2–5 minutes),[10] produces robust analgesia (with an equianalgesic ratio to morphine of 1:1.5–2),[11] and its κ-receptor agonism may confer selective visceral pain inhibition and potentially reduce visceral traction responses. Notably, oxycodone may also lower the incidence of PONV.[12,13] These characteristics suggest that oxycodone holds promise for analgesia in abdominal surgery and endoscopic procedures.[14]

Despite these theoretical advantages, the optimal intravenous dose of oxycodone for painless colonoscopy remains unclear. Most existing reports are either small-scale observational studies or involve considerable variation in drug combination regimens.[15] Systematic evaluation of the dose-response relationship specifically for analgesia during colonoscopy is lacking. Considering the special features of colonoscopic procedures—such as relatively short duration, distinctive stimulation patterns (eg., luminal insufflation, scope navigation through flexures, mesenteric traction)—it is vital to establish an accurate and effective dosing range for oxycodone to optimize anesthetic management in painless colonoscopy.[16] Underdosing risks inadequate analgesia, procedural interference, or the need for additional propofol (increasing overall risk); overdosing, on the other hand, can result in unnecessary opioid-related side effects (such as respiratory depression or excessive sedation).[17]

Therefore, the aim of this study was to systematically assess the dose-response relationship of intravenous oxycodone for providing satisfactory analgesia in patients undergoing painless colonoscopy, and to precisely determine its median effective dose (ED_{50}). To achieve this efficiently with a limited sample size, we employed the Dixon up-and-down sequential allocation method. In this design, the dose administered to each subsequent patient is determined by the response of the previous patient: the dose is increased if the prior response indicates inadequate analgesia and decreased if the response indicates adequate analgesia. The findings of this research are intended to provide crucial evidence for the safe, effective, and individualized use of oxycodone in clinical practice, thereby optimizing sedation and analgesia protocols for painless colonoscopy.

Methods

Study Design and Participants

This prospective, single-center, dose-finding study utilized the Dixon "up-and-down" sequential allocation method to determine the optimal dose of oxycodone for sedation and analgesia in patients undergoing painless colonoscopy performed outside the operating room. The study protocol was approved by the Institutional Review Board of Tianjin Jizhou District People's Hospital on October 23, 2023 (Approval No. IRB2023-18) and was registered in the Chinese Clinical Trial Registry on November 9, 2023 (Registration No. ChiCTR2300077446). This work represents the preliminary dose-finding phase of the overall research plan as outlined in the clinical trial registration. The study was conducted in strict accordance with the principles of the Declaration of Helsinki, and all participants provided written informed consent prior to enrollment.

Inclusion criteria were as follows: (1) patients scheduled for elective fiberoptic colonoscopy under intravenous anesthesia in the endoscopy suite, (2) patient's explicit request for intravenous anesthesia, (3) age between 18 and 65 years, (4) American Society of Anesthesiologists (ASA) physical status classification I or II, and (5) signed informed consent. Exclusion criteria included: (1) history of neurological or psychiatric diseases; (2) known drug allergies; (3) any surgery within the previous month; (4) chronic use of analgesics or medications that could affect study outcomes; (5) uncontrolled hypertension, arrhythmias, or congestive heart failure; (6) diagnosis of obstructive sleep apnea syndrome (OSA), acute upper respiratory tract infection, bronchial asthma, or other relevant respiratory disorders; (7) history of malignancy or active cancer treatment; and (8) any other condition deemed unsuitable for participation by the investigators.

Anesthesia and Intervention Protocol

Participants fasted according to standard protocols prior to the procedure. Based on preliminary experiments, the initial dose of oxycodone was set at 0.07 mg/kg. The study employed the Dixon "up-and-down" sequential allocation method to

titrate the oxycodone dose individually. The starting dose for the first patient was 0.07 mg/kg, administered intravenously two minutes before induction. Two minutes after oxycodone administration, all patients received propofol target-controlled infusion (TCI) using the Marsh model: an initial plasma target concentration of 4 μg/mL was administered intravenously. Once a Ramsay sedation score of II was achieved, positive pressure ventilation via facemask was instituted, and the propofol plasma target concentration was reduced to 2.5 μg/mL for maintenance by continuous infusion throughout the colonoscopy.

Assessment of Movement Response and Oxycodone Dose Adjustment

The primary efficacy endpoint was the patient's body movement response during the insertion of the colonoscope, graded as follows:

Grade I: Minor involuntary limb movement, not interfering with endoscopy; no additional propofol required. Grade II: Significant agitation affecting endoscopy; additional anesthesia required to suppress movement. Grade III: Severe agitation, unable to cooperate; procedure termination, deeper anesthesia required before resuming examination.

Body movement ≥ Grade II at the time of colonoscope insertion was considered a positive response; otherwise, the response was negative. According to the Dixon up-and-down method, if the previous patient exhibited a positive response, the subsequent patient received oxycodone at an increased dose (increment of 0.01 mg/kg). Conversely, a negative response resulted in a decrease of 0.01 mg/kg for the next patient. The sequential allocation continued until the 7th reversal from negative to positive was observed, at which point the trial ended. The effective dose (ED50) and corresponding 95% confidence intervals were determined.

Data Collection

Demographic and Baseline Data

Demographic data including gender, age, weight, ASA physical status, duration of anesthesia (from induction to awakening), and total colonoscopy duration were recorded for all participants.

Primary Outcome

Total usage of opioid analgesics (oxycodone, with conversion to morphine milligram equivalents where applicable).

Secondary Outcomes

Hemodynamic and respiratory variables (mean arterial pressure, heart rate, SpO_2, respiratory status—need for facemask ventilation or endotracheal intubation) recorded at the following time points: immediately before (T1), two minutes after (T2), at admission (T3), after reaching the splenic (T4) and hepatic flexure (T5), upon arrival at the ileocecal area (T6), and during endoscopic withdrawal (T7).Movement response grading at T3.

Incidence of adverse events within 20 minutes after procedure completion, including agitation, abdominal pain, nausea/vomiting, dizziness/headache, postural instability, and other relevant symptoms.

Statistical Analysis

All statistical analyses were performed using SPSS version 25.0 (SPSS Inc., Armonk, NY, USA). Data normality was assessed using the Kolmogorov–Smirnov test. Continuous variables with normal distribution are presented as mean ± standard deviation (SD), while those with non-normal distribution are expressed as median (interquartile range, IQR). Categorical variables are summarized as frequencies and percentages.

The up-and-down sequential allocation method of Dixon and Massey was utilized to estimate the median effective dose (ED_{50}) of oxycodone required to suppress body movement during painless colonoscopy. In this study, patients received incremental or decremental doses of oxycodone based on the movement response observed during colonoscope insertion.

A positive response was defined as a movement score ≥ 2, while a negative response was defined as a movement score < 2. The dose for the subsequent patient was increased by 0.01 mg/kg if the previous response was positive and decreased by 0.01 mg/kg if the response was negative.

Reversal points were identified by examining where the response changed from positive to negative or negative to positive in consecutive patients. The ED_{50} was then calculated as the mean of the oxycodone doses at these crossover points.

The standard error (SE) and 95% confidence interval (CI) for ED_{50} were calculated as follows:

$SD=\sum i=1n(xi-\mu)2n-1SD=i=1n(xi-\mu)2n-1$

where SD is the standard deviation of the reversal point doses, and n is the number of reversals. The CI was determined using the formula:

95% CI = ED50 ± t(n−1),0.975 × SE

where t(n−1),0.975 is the t-value from the t-distribution table for n-1 degrees of freedom.

Results

Patient Enrollment and Demographics

A total of 40 patients were initially enrolled in the study, with 36 patients completing the study per protocol. The patients were divided into groups based on the sedation protocol used during their colonoscopy procedures (see Figure 1). The demographic data collected included age, height, and weight (see Table 1).

ED50 Calculation

A total of 36 patients were included in the analysis. According to the Dixon up-and-down method, 14 reversal points were identified where the response switched between positive (movement) and negative (no movement). The doses at these reversal points are listed in Table 2. Responses of 36 consecutive patients according to the Dixon up–down method and the dose of oxycodone and indicates 7 crossovers in each group crossing from movement score ≥2 (empty circle) to movement score < 2 (filled circle) (see Figure 2).

The ED_{50} was calculated as the mean dose of these 14 reversal points:

ED50=xin=0.7714=0.055 mg/kg

The standard deviation (SD) and standard error (SE) were 0.0133 and 0.0036, respectively. The 95% confidence interval (CI) was calculated using the t-distribution (df=13, t=2.160):

95% CI=0.055±2.160×0.0036=[0.047,0.063] mg/kg

Therefore, the estimated ED_{50} of oxycodone for suppression of body movement during colonoscope insertion was 0.055 mg/kg (95% CI: 0.047–0.063 mg/kg).

Hemodynamic Monitoring and Adverse Events

Hemodynamic stability was assessed by measuring mean blood pressure (MBP) and heart rate (HR) at specific intervals: immediately before (T1), two minutes after (T2), at admission (T3), after reaching the splenic (T4) and hepatic flexure

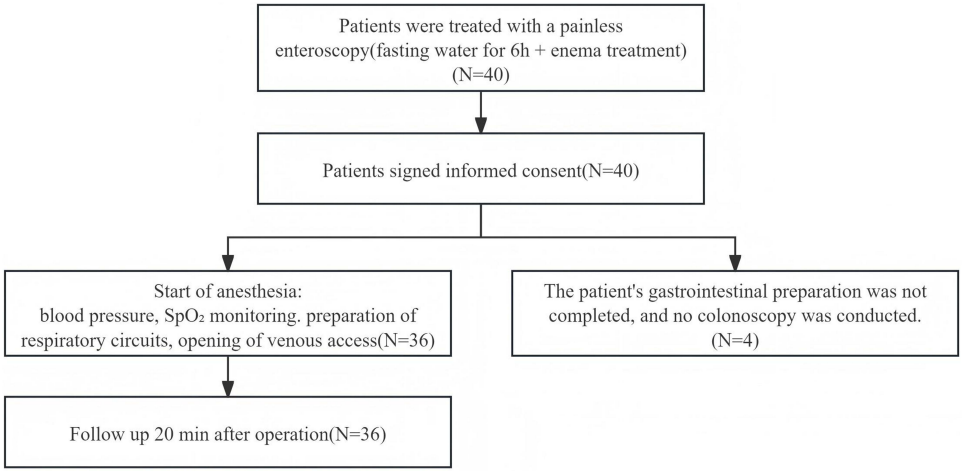

Figure 1 Study flow chart.

Table 1 Baseline Characteristics (n=36)

Variable	Minimum	Maximum	Mean	Standard Deviation
Age (yr)	29.00	69.00	52.27	10.05
BMI (kg/m^2)	16.00	27.65	23.89	3.97
The total amount of propofol (mg)	20.00	150.00	61.62	28.04
Duration of anesthesia (min)	10.00	55.00	21.81	9.63
Duration of colonoscopy (min)	5.00	41.00	17.27	8.36

Table 2 Doses of Oxycodone at Reversal Points

Patients' ID	**5**	**6**	**9**	**10**	**14**	**15**	**17**
Reversal Point Dose (mg/kg)	0.07	0.08	0.05	0.06	0.04	0.05	0.03
Response	Positive	Negative	Positive	Negative	Positive	Negative	Positive
Patients' ID	**18**	**21**	**22**	**28**	**29**	**35**	**36**
Reversal Point Dose (mg/kg)	0.04	0.05	0.06	0.06	0.07	0.05	0.06
Response	Negative	Positive	Negative	Positive	Negative	Positive	Negative

(T5), upon arrival at the ileocecal area (T6), and during endoscopic withdrawal (T7)(see Table 3 and Figure 3). Adverse events were closely monitored, focusing on respiratory depression, postoperative nausea and vomiting (PONV), and other opioid-related side effects. Notably, 2 cases of respiratory depression were observed. And PONV was reported in 1 patient and she went into remission 20 minutes later.

Spearman Correlation Between Demographics and Analgesic Consumption

Spearman correlation analysis showed that analgesic consumption was negatively correlated with sex ($\rho = -0.364$, $P = 0.137$), and positively correlated with age ($\rho = 0.189$, $P = 0.452$) and BMI ($\rho = 0.411$, $P = 0.090$). Notably, BMI exhibited a trend toward a positive association with analgesic consumption.However, none of these correlations reached statistical significance ($P > 0.05$) (Figure 4).

Discussion

This prospective study utilized the Dixon up-and-down sequential allocation method to precisely determine the median effective dose (ED_{50}) of intravenous oxycodone for suppressing body movement during painless colonoscopy under non-operating room anesthesia (NORA). Our results identified an ED_{50} of 0.055 mg/kg (95% CI: 0.047–0.063 mg/kg) when

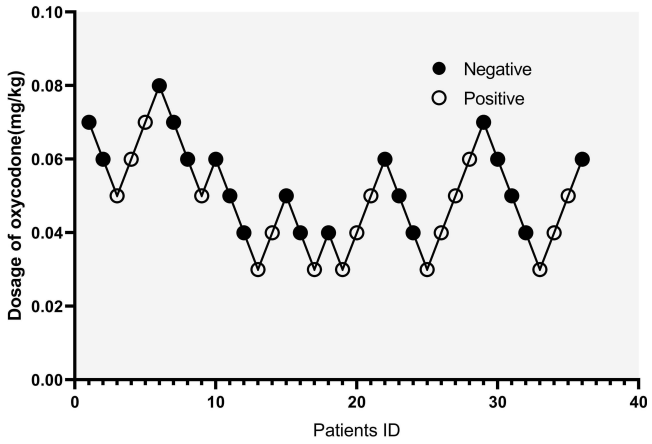

Figure 2 Staircase plot of oxycodone dosing. Empty circles indicate positive responses (movement score ≥2), filled circles indicate negative responses (movement score <2).

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Table 3 Vital Signs During Anesthesia (n=36, Mean±SD)

	T1	T2	T3	T4	T5	T6	T7
MAP /mmHg	87.16±13.93	73.49±14.93	68.68±10.77	68.73±12.70	70.43±16.44	68.81±11.74	69.76±12.90
SpO_2/%	98.70±1.47	98.41±1.57	97.24±2.34	97.00±2.35	97.16±2.42	97.70±1.90	97.54±1.92
HR /beats/min	78.46±14.38	76.19±12.73	75.70±11.34	71.27±10.17	71.43±11.26	71.51±8.97	71.27±10.37

combined with a fixed propofol regimen. This finding provides a critical, evidence-based dosing reference for oxycodone in this setting, addressing a significant gap where previous studies often relied on empirical or fixed-dose regimens.[15]

Comparison with Published ED_{50} Values of Oxycodone in Different Surgical Contexts

The ED_{50} value obtained in our study is considerably lower than those reported for more painful procedures. For instance, Kang et al demonstrated that the ED_{50} of oxycodone for blunting the hemodynamic response to tracheal intubation was 0.254 mg/kg in women and 0.324 mg/kg in men.[18] Similarly, Yu et al reported ED_{50} values ranging from 0.060 to 0.092 mg/kg for postoperative analgesia after gynecological surgeries when combined with local ropivacaine wound infiltration.[19] The lower ED_{50} in our study (0.055 mg/kg) likely reflects the fundamentally different nature of painless colonoscopy: the procedure is diagnostic rather than incisional, the duration is short, and the primary noxious stimulus is visceral distension rather than surgical incision or tracheal manipulation. This comparison underscores the importance of context-specific dose determination rather than extrapolating doses from other surgical settings.

Mechanistic Advantages of Oxycodone for Visceral Analgesia in Colonoscopy

A key strength of our study lies in the selection of oxycodone, whose pharmacological profile is uniquely suited for gastrointestinal procedures. Oxycodone is distinguished as a dual agonist at both μ- and κ-opioid receptors. While traditional opioids like sufentanil and fentanyl primarily target μ-receptors, oxycodone's significant affinity for κ-receptors offers a distinct advantage in managing visceral pain. As highlighted by Yu et al, κ-receptor activation selectively inhibits visceral nociceptive transmission without adversely affecting gastrointestinal motility.[19] Chen et al also demonstrated that the combination of oxycodone (0.10 mg/kg) with propofol effectively suppressed visceral pain responses during abortion procedures, with anxious patients requiring higher propofol doses (ED_{50} 2.42 mg/kg vs. 1.96 mg/kg).[20] This mechanism likely explains the effective suppression of movement responses induced by colonic distension and mesenteric traction in our study, even at the relatively low dose of 0.055 mg/kg.

Influence of Demographic Factors on Oxycodone Requirement

Our Spearman correlation analysis showed a trend toward a positive association between BMI and analgesic consumption ($\rho = 0.411$, $P = 0.090$), although this did not reach statistical significance. This finding aligns with the work of Kang et al, who

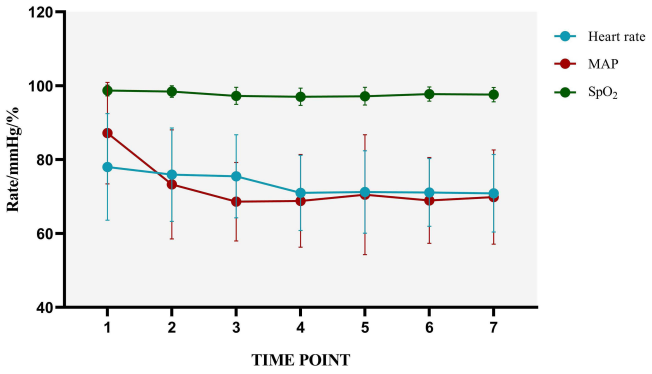

Figure 3 Hemodynamic changes at different time points. Data are presented as the mean ± standard deviation. HR indicates heart rate; MAP, mean blood pressure; SpO2, oxygen saturation. Immediately before (T1), two minutes after (T2), at admission (T3), after reaching the splenic (T4) and hepatic flexure (T5), upon arrival at the ileocecal area (T6), and during endoscopic withdrawal (T7).

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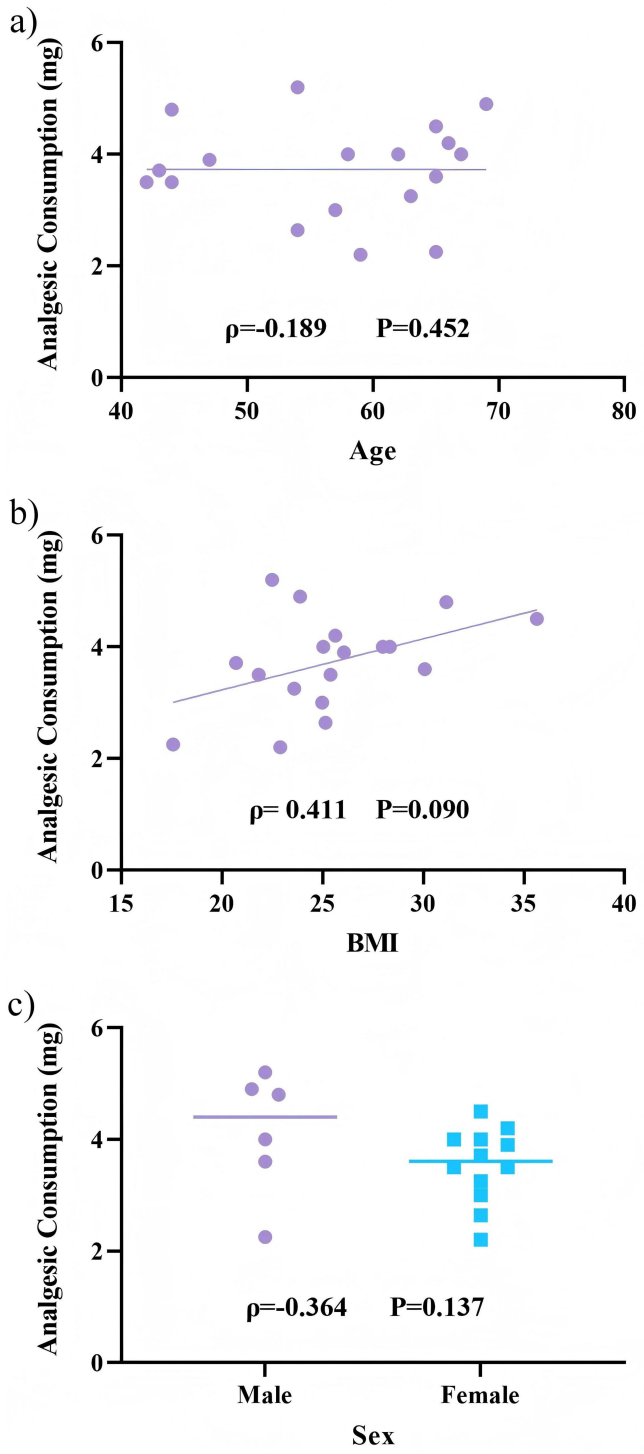

Figure 4 Correlation of Analgesic Consumption with Sex, Age, and BMI. (**a**) Age, (**b**) BMI, (**c**) Sex.

demonstrated that gender significantly affects oxycodone ED_{50}, with men requiring approximately 28% more oxycodone than women for blunting intubation reactions.[18] Similarly, Zhang et al highlighted that age-related pharmacodynamic changes—including decreased μ-opioid receptor density and altered blood-brain barrier permeability—increase CNS drug sensitivity in elderly patients.[21] While our study was not powered to detect subgroup differences, the observed trends suggest that individualized dosing based on BMI and gender warrants further investigation in larger cohorts.

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Safety Profile and Hemodynamic Stability

Our hemodynamic data demonstrated stable mean arterial pressure, heart rate, and SpO_2 across all dosage steps, with no clinically significant hypotension, bradycardia, or hypoxemia. This stability aligns with the "propofol-sparing" effect of oxycodone. Yu et al similarly reported that a single intravenous injection of oxycodone caused only acceptable decreases in mean blood pressure and heart rate within a short time.[19] Importantly, the incidence of respiratory depression in our study (2/36, 5.6%) was considerably lower than that reported by Kang et al (66.7%), who defined respiratory depression as a respiratory rate <10 breaths/min following rapid bolus injection.[18] This discrepancy likely reflects differences in definition, patient population (healthy NORA patients vs. general anesthesia with intubation), and the fact that our patients received supplemental oxygen via nasal cannula.

The Role of Operator Experience as a Confounding Variable

We acknowledge that procedural discomfort and duration depend on the expertise of endoscopists. Although all colonoscopies in our study were performed by experienced endoscopists (each having completed >500 procedures), we did not quantitatively assess individual operator expertise or the exact duration of colonoscope insertion. Both factors could influence the degree of patient discomfort and the required analgesic dose. This represents a potential confounding variable that should be controlled in future studies by stratifying for operator experience or using standardized procedure durations.

Limitations

Several limitations warrant consideration. First, our study population was restricted to healthy adults (ASA I–II) aged 18–65 years, excluding cancer patients. Consequently, these findings may not be generalizable to elderly patients (≥65 years), who often exhibit altered pharmacokinetics and increased sensitivity to opioids, as emphasized by Zhang et al,[21] or to patients with severe comorbidities (ASA III or higher) Second, as a dose-finding study using the Dixon method, our sample size was calculated specifically for estimating the ED_{50} and was not powered to detect rare adverse events or subtle differences in secondary outcomes. Third, the single-center design may introduce selection bias. Fourth, we did not quantitatively assess operator expertise or procedure duration, which are potential confounding variables. Finally, the primary endpoint—body movement graded as ≥2—was inherently subjective, although assessed by a single experienced anesthesiologist to ensure consistency.

Conclusion

In conclusion, this study determined the ED_{50} of intravenous oxycodone to be 0.055 mg/kg (95% CI: 0.047–0.063 mg/kg) for suppressing movement during painless colonoscopy under NORA when combined with propofol. The oxycodone-propofol regimen demonstrated excellent hemodynamic stability and effective analgesia without significant respiratory depression. These findings establish oxycodone as a safe and effective alternative to traditional opioids for visceral analgesia in this setting, providing a precise evidence-based dosing reference for clinical practice.

Data Sharing Statement

The authors intend to share individual deidentified participant data from the present study. The specific data to be shared include patients' gender, age, oxycodone dosage administered, and vital signs recorded during the research process. No additional study-related documents will be made available to the public. The aforementioned deidentified participant data is available as Table S1, and will be publicly accessible from the date of the article's publication with permanent availability for scientific research purposes. Correspondence for data access can be directed to the corresponding author: Yan Li, E-mail: drliyanteam@163.com.

Disclosure

The authors report no conflicts of interest in this work.

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