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Differential dosing of oxycodone in combination with propofol in diagnostic painless gastroscopy in elderly patients

A prospective randomized controlled trial

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Abstract

Objective: The aim of this study is to investigate the safety and efficacy of different doses of oxycodone in combination with propofol during painless gastroscopy.

Methods: 120 patients underwent painless gastroscopy under general anesthesia. According to the different doses of oxycodone, patients were divided into 4 groups, group A (oxycodone 0.025 mg/kg + propofol), group B (oxycodone 0.05 mg/kg + propofol) and group C (oxycodone 0.1 mg/kg + propofol), control group (propofol alone), with 30 cases in each group. The general characteristics of all patients were then evaluated. Mean arterial pressure (MAP), heart rate (HR) and peripheral capillary oxygen saturation (SpO2) were recorded at different time points, including the time before anesthesia (T0), failure of the lash reflex (T1), successful placement of the mirror (T2), removal of the mirror (T3) and waking up (T4). The intraoperative propofol dosage and the operative time of gastroscopy were recorded. The occurrence of adverse effects in the 4 groups was also compared.

Results: General characteristics, gastroscopy operative time and SpO2 did not differ significantly between the 4 groups ($P > .05$). However, group C had the lowest amount of propofol during gastroscopy ($P < .05$). At T1, groups A, B, and C had a faster HR than the control group ($P < .05$). At T2, groups A, B, and C had a lower MAP than the control group ($P < .05$). Groups B and C had fewer adverse effects than groups A and the control group ($P < .05$). Importantly, groups B and C had a shorter recovery time than groups A and the control group ($P < .05$), but no statistically significant differences were found between groups B and C.

Conclusion: 0.05 mg/kg oxycodone in combination with propofol can be used safely and effectively for painless gastroscopy, with the advantages of a low propofol dose, maintenance of hemodynamic stability and few adverse effects.

Abbreviations: ASA = American society of anesthesiologists, HR = heart rate, MAP = mean arterial pressure, SpO_2 = peripheral capillary oxygen saturation, T0 = time before anesthesia, T1 = failure of the lash reflex, T2 = successful placement of the mirror, T3 = removal of the mirror, T4 = waking up.

Keywords: adverse effects, oxycodone, painless gastroscopy, propofol

1. Introduction

Gastroscopy is a common method in clinical practice for the diagnosis of gastrointestinal diseases, characterized by high accuracy and safety.[1] However, insertion of the gastroscope often causes severe discomfort in the patient's throat, leading to various adverse effects, such as violent retching, nausea, or vomiting. In addition, the procedure often leads to increased release of catecholamines in the patient's body, resulting in increased heart rate, blood pressure and cardiac arrhythmias, which can even lead to serious complications including angina, myocardial infarction, stroke or cardiac arrest.[2] In contrast, painless gastroscopy is now widely used because it significantly reduces the patient's pain and has fewer adverse effects.[3–5]

Propofol is the preferred intravenous anesthetic for painless gastroscopy. It has the advantage of a rapid onset of action and a short duration of action. However, when propofol is used alone, higher doses are usually required to achieve a satisfying anesthesia depth, which increases the risk of deeper sedation and delayed awakening.[6–10] In addition, propofol has the disadvantage of poor analgesia, induces choking and body movement reactions, which increases the risk of adverse events during gastroscopy. Researchers have reported the use

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of alfentanil or fentanyl or midazolam or remifentanil in combination with propofol to reduce the dosage of propofol and thus reduce the incidence of adverse events during gastroscopic procedures.[11–14] Nevertheless, adverse events have occasionally occurred.

Oxycodone was first synthesized in Germany in 1916 and is classified as a semisynthetic opioid chemically similar to morphine, which has been approved by the United States Food and Drug Administration (FDA) as a Schedule II narcotic.[15] Oxycodone belongs to the family of the most potent analgesic compounds available for the treatment of moderate to severe pain. It acts not only on μ-opioid receptors on the presynaptic membrane of the central nervous system to exert neuropathic analgesic effects but also on κ-receptors on smooth muscle to exert analgesic effects on visceral pain,[16,17] with the advantages of a rapid onset of action and mild adverse effects.[18–22]

Currently, the application of oxycodone to reduce propofol-induced adverse effects in painless gastroscopic anesthesia is still very rare. Moreover, the question of at what dose oxycodone in combination with propofol can maximize the suppression of the occurrence of adverse effects remains unresolved. We hypothesized that the use of oxycodone would inhibit the adverse effects of propofol alone and also investigated the optimal dose of oxycodone in combination with propofol that would minimize the occurrence of adverse effects during painless gastroscopy.

2. Materials and Methods

2.1. Ethics

All patients who participated in the study had signed an informed consent form. The study was also approved by the Ethics Committee of the Third Hospital of Qinhuangdao (No. 2019-18).

2.2. General characteristics

We selected 120 patients who underwent painless gastroscopy from January 2019 to January 2021 at the Third Hospital of Qinhuangdao City, Hebei Province, China. A randomized block design was used, and then patients were randomly divided into 4 groups according to the different application doses of oxycodone, namely group A (oxycodone 0.025 mg/kg + propofol), group B (oxycodone 0.05 mg/kg + propofol) and group C (oxycodone 0.1 mg/kg + propofol), control group (propofol alone), with 30 cases in each group. Then the sex, age, weight and American Society of anesthesiologists (ASA) classification of the patients were recorded.

Inclusion criteria: Patients need a gastroscopy for digestive tract examination; patients who required painless gastroscopy or treatment; age ≥ 60 years; ASA classification I or II grade. Exclusion criteria: age < 60 years; patients with a history of severe hypertension, diabetes mellitus or coronary artery disease; patients with a history of allergy to oxycodone and propofol; patients with chronic respiratory insufficiency (oxygen saturation < 95); patients with impaired speech function or mental disorders; severe coagulation abnormalities.

2.3. Anesthetic methods

Before gastroscopy, patients were not given food and water for at least 8 hours. After admission to the operating room, the patient's vital signs were continuously monitored, including blood pressure, heart rate, respiration, and oxygen saturation. A peripheral venous line was then established and oxygen was administered through a mask (oxygen flow rate of 2–5 L/min).

Before anesthesia, oxycodone 0.025 mg/kg, 0.05 mg/kg, 0.1 mg/kg, and an equal amount of saline were slowly administered intravenously to the 4 groups of patients according to their body weight. Two minutes later, propofol 1 to 2 mg/kg was administered to all patients.

Painless gastroscopy was performed after the disappearance of the lash reflex. Propofol (0.08 mg/kg/min) was pumped continuously during the procedure to maintain anesthesia, and the pumping of propofol was stopped at the end of the examination. To avoid bias in experimental results due to differences between operators, all patients were anesthetized by the same anesthetist, and gastroscopy was performed by the same experienced physician

Propofol 0.5 mg/kg was administered if a significant body movement response was detected during painless gastroscopy; if intraoperative respiratory depression was detected, that is (SpO_2: ≤90%), oxygen was administered under mask pressure to assist breathing; in case of hypotension (systolic blood pressure ≤ 90 mm Hg or less than 20% of baseline), ephedrine 5 mg was administered intravenously; in case of bradycardia (HR < 50 beats/min), atropine 0.5 mg was administered intravenously.

2.4. Evaluation indicators

We assessed indicators at 5 time points during surgery, including time before anesthesia (T_0), loss of eyelash reflex (T_1), successful mirror placement (T_2), mirror removal (T_3) and waking (T_4). Subsequently, MAP, HR, and SpO_2 were recorded at T_0, T_1, T_2, T_3, and T_4. Intraoperative propofol dosage and gastroscopy operating time were recorded for each group. We also recorded the adverse effects, including hypotension, bradycardia, respiratory depression, body movement response, and nausea and vomiting, that occurred in the 4 groups during the study and compared the frequency of adverse effects in each group. In addition, we evaluated the time from the end of surgery until the patients fully woke up. The wake-up score included 3 items: Degree of wakefulness, degree of airway patency and limb mobility. Specifically: degree of wakefulness: 2 points for fully waking up, 1 point for responding to stimuli and 0 point for no response to stimuli; degree of airway patency: 2 points for coughing on doctor's orders, 1 point for maintaining airway patency without the support and 0 point for airway requiring support; degree of limb mobility: 2 points for conscious limb movement, 1 point for unconscious limb movement and 0 points for no limb movement. We defined a score of 6 as a full awakening of the patient according to the Steward Score.[23]

2.5. Statistical analysis

We used SPSS (version 26.0) for data analysis. Normality was tested using the Kolmogorov-Smirnov test for continuous variables. For data that conformed to a normal distribution, differences between groups were tested using ANOVA; for data that did not conform to a normal distribution, non-parametric tests were used. Statistical data were expressed as percentages (%) and the χ^2-test was used for comparison between groups. $P < .05$ means that the difference is statistically significant.

3. Results

3.1. General characteristics

A total of 120 patients were included in the study. Details of age, sex, weight and ASA classification of the 4 groups are shown in Table 1. The results showed that there were no statistically significant differences in the general characteristics between the groups ($P > .05$). In addition, there was no significant difference in gastroscopy operation time among the 4 groups ($P > .05$).

Table 1

General characteristics of patients in the 4 groups.

Indicators	Group A	Group B	Group C	Group control	*P* value
Male (n, %)	16 (53.33)	13 (43.33)	14 (46.67)	15 (50.00)	.88
Age (yrs)	48.23 ± 6.81	49.10 ± 6.78	50.53 ± 7.09	47.70 ± 7.31	.44
Weight (kg)	71.43 ± 8.97	69.33 ± 9.57	70.47 ± 11.41	69.70 ± 8.47	.85
ASA					
I (n, %)	17 (56.67)	19 (63.33)	16 (53.33)	20 (66.67)	.71
II (n, %)	13 (43.33)	11 (36.67)	14 (46.67)	10 (33.33)	
Operation time (min)	6.2 ± 1.3	5.9 ± 1.5	5.7 ± 1.1	6.0 ± 1.1	.56

ASA = American society of anesthesiologists.

P < .05 means the difference is statistically significant.

3.2. Dose of propofol and time to awakening in the 4 groups

Table 2 shows the propofol doses used and the time from the end of gastroscopy to the full awakening of the patients (awakening grade score of 6) in the 4 groups. The results showed that the intraoperative propofol dosage was significantly lower in groups A, B, and C than in group control, with group C receiving the lowest amount of propofol ($P < .05$). In addition, the time to full awakening was significantly shorter in groups A, B, and C than in group control, with group C having less time to full awakening than groups A and B ($P < .05$).

3.3. MAP

MAP results at T_1-T_3 were significantly lower than at T_0 in all groups ($P < .05$). At T_2, groups A, B and C have lower MAP than groups control ($P < .05$) (Table 3).

3.4. HR

Groups A, B, and C have slower HR at T_1-T_3 than at T_0 ($P < .05$); at T_1, groups A, B, and C had a faster HR than group control ($P < .05$) (Table 4).

3.5. SpO_2

No significant difference was found between T_1-T_4 and T_0 among 4 groups ($P > .05$). The details are shown in Table 5.

3.6. Adverse effects

Groups B and C have significantly lower occurrence of hypotension and body movement reactions than groups A and control ($P < .05$). Besides, Groups A, B, and C have significantly lower bradycardia than group control ($P < .05$). Moreover, the incidence of hypoxia and vomiting was slightly higher in the group control than in group B, but these differences were not statistically significant ($P > .05$) (Table 6).

4. Discussion

Painless gastroscopy is an important diagnostic and therapeutic technique for diseases of the digestive tract. It has evolved from the initial common ulcer diagnosis to complex therapeutic procedures that include endoscopic hemostasis, foreign body removal, endoscopic mucosal resection, endoscopic submucosal dissection, endoscopic retrograde cholangiopancreatography, gastrointestinal strictures and natural orifice transluminal endoscopic surgery.[1,3,14] The complex procedures make anesthesia essential. Otherwise, surgery has to be interrupted due to violent body movements of patients because they cannot bear the discomfort, which increases the risk of mucosal damage, bleeding and perforation of the digestive tract.[24] To date, more and more elderly patients suffer from digestive tract problems. This presents a challenge for endoscopic anesthesia, as elderly patients are more likely to have cardiopulmonary disease.[25] In these patients, sedation should be performed with caution, especially regarding the dose and speed of administration of the drugs used.

Propofol is a short-acting intravenous anesthetic made from alkyl acids. It is characterized by a rapid onset of action, a strong sedative effect and a short recovery time after withdrawal of the drug.[26] If the dosage is too high or administered too quickly, respiratory or circulatory depression may occur, characterized by reduced respiratory rate or apnea and hypotension. Although propofol can cause hemodynamic fluctuations—which is more likely in elderly patients as most of them have cardiopulmonary disease—its good sedative and anesthetic effects still make propofol the most important anesthetic for painless gastroscopy. However, it should be noted that propofol has no analgesic effect, so it must be combined with opioids for sedation anesthesia in painless gastroscopy. Currently, there are many reports on the use of controlled-release oxycodone tablets for postoperative analgesia, especially for the treatment of moderate to severe cancer pain, but few reports on the use of oxycodone intravenously for intraoperative analgesia and painless endoscopy.

The first important finding of this study is that oxycodone improves the hemodynamic stability of propofol anesthesia during painless gastroscopy in chronic liver disease. This study compared the anesthetic effects of painless gastroscopy at different anesthetic phases (T_1-T_4 vs T_0). The results showed that MAP and HR were significantly lower at T_1-T_3 than at T_0 in each group; moreover, MAP and HR were significantly higher in the 3 groups using oxycodone than in the control group at T_1-T_3. This result suggests that gastroscopy may cause stress and hemodynamic fluctuations in the body, but oxycodone in combination with propofol may reduce hemodynamic fluctuations in the body and improve the safety of the procedure. In addition, no significant differences were found in the results of MAP and HR of the 3 groups A, B, and C when compared at different time points. This suggests that the different doses of oxycodone had minimal hemodynamic effects on the gastroscopy patients.

Table 2

Propofol dosage and time to complete awakening in each group.

Indicators	Group A	Group B	Group C	Group control	*P* value	Post hoc test (*P* < .05)
Propofol dosage (mg)	145.8 ± 19.8	141.3 ± 17.9	134.3 ± 23.5	175.9 ± 20.7	.000	Group A vs Group C, Group A vs Group Control, Group B vs Group Control, Group C vs Group Control
Recovery time (min)	3.5 ± 0.9	3.2 ± 0.8	2.6 ± 0.6	4.32 ± 1.02	.000	Group A vs Group C, Group A vs Group Control, Group B vs Group C, Group B vs Group Control, Group C vs Group Control

P < .05 means the difference is statistically significant.

Table 3

The outcomes of mean arterial pressure in each group at the different times of anesthesia.

Times	Group A	Group B	Group C	Group control	*P* value	Post hoc test (*P* < .05)
T_0	88.3 ± 8.6	86.8 ± 7.1	87.2 ± 7.6	90.6 ± 7.2	.23	
T_1	77.1 ± 8.3	78.2 ± 9.3	76.7 ± 7.7	77.4 ± 5.9	.91	
T_2	75.5 ± 8.1	75.6 ± 4.8	74.8 ± 6.3	80.1 ± 6.9	.01	Group A vs Group Control, Group B vs Group Control, Group C vs Group Control
T_3	77.4 ± 10.7	77.0 ± 6.6	77.5 ± 8.7	80.4 ± 8.4	.42	
T_4	87.3 ± 8.5	85.8 ± 8.5	86.9 ± 8.1	85.5 ± 6.1	.78	

T0 = time before anesthesia, T1 = failure of the lash reflex, T2 = successful placement of the mirror, T3 = removal of the mirror, T4 = waking up.
P < .05 means the difference is statistically significant.

Table 4

Comparison of heart rate of patients in 4 groups at different anesthetic phases.

Times	Group A	Group B	Group C	Group control	*P* value	Post hoc test (*P* < .05)
T_0	73.7 ± 9.6	74.0 ± 12.6	74.4 ± 8.5	75.6 ± 7.7	.88	
T_1	64.9 ± 6.3	64.7 ± 7.2	65.0 ± 8.5	58.4 ± 5.1	.00	Group A vs Group Control, Group B vs Group Control, Group C vs Group Control
T_2	65.3 ± 6.6	65.6 ± 6.7	65.3 ± 8.1	66.1 ± 8.4	.97	
T_3	64.4 ± 6.5	63.1 ± 4.6	66.4 ± 8.5	64.6 ± 7.8	.37	
T_4	66.6 ± 11.2	73.9 ± 5.5	72.5 ± 6.1	71.2 ± 9.9	.01	Group A vs Group B

T0 = time before anesthesia, T1 = failure of the lash reflex, T2 = successful placement of the mirror, T3 = removal of the mirror, T4 = waking up.
P < .05 means the difference is statistically significant.

Table 5

The results of peripheral capillary oxygen saturation in 4 groups at the different times.

Times	Group A	Group B	Group C	Group control	*P* value
T_0	97.5 ± 1.3	97.9 ± 1.2	97.2 ± 1.1	98.1 ± 0.9	.12
T_1	96.2 ± 2.6	95.6 ± 2.9	96.2 ± 2.7	96.4 ± 2.6	.17
T_2	98.2 ± 1.6	98.0 ± 1.2	97.6 ± 2.0	97.8 ± 1.8	.40
T_3	97.8 ± 1.5	98.1 ± 1.5	97.2 ± 1.3	97.7 ± 1.8	.15
T_4	97.9 ± 0.9	97.8 ± 1.1	97.5 ± 1.4	98.3 ± 0.7	.07

T0 = time before anesthesia, T1 = failure of the lash reflex, T2 = successful placement of the mirror, T3 = removal of the mirror, T4 = waking up.*P* < .05 means the difference is statistically significant.

Table 6

The incidence of adverse events in different groups.

Groups	Hypotension (%)	Bradycardia (%)	RD (%)	NV (%)	BMR (%)
Group A	4 (13.3)	1 (3.3)	3 (10.0)	1 (3.3)	8 (26.7)
Group B	1 (3.3)	0 (0.0)	1 (3.3)	1 (3.3.)	2 (6.7)
Group C	0 (0.0)	0 (0.0)	2 (6.7)	4 (13.3)	0 (0.0)
Group Control	6 (20.0)	8 (26.7)	5 (16.7)	6 (20.0)	14 (46.7)
P value	.02	.00	.40	.10	.00

BMR = body movement reaction, NV = nausea and vomiting, RD = respiratory depression.
P < .05 means the difference is statistically significant.

The second major finding of this study is that 0.05 mg/kg oxycodone in combination with propofol had the best anesthetic effect, the least amount of propofol required, the shortest time to full awakening and the fewest adverse effects. To determine the most appropriate dose of oxycodone for painless gastroscopy in elderly patients, we studied the analgesic effect of 3 different doses of oxycodone

Regarding the propofol dose, the results showed that group C (0.1 mg/kg oxycodone) had the lowest propofol dose, followed by group B (0.05 mg/kg oxycodone). Regarding time to full awakening, we assessed the effect of oxycodone on respiration by observing the duration of full awakening and found that groups B (0.05 mg/kg oxycodone) and C (0.1 mg/kg oxycodone) had a shorter time to full awakening than the other 2 groups ($P < .05$), but there was no significant difference between group B and group C ($P > .05$), suggesting that increasing the oxycodone dose beyond 0.05 mg/kg did not further reduce the time to full awakening of patients. Regarding the occurrence of adverse effects, we found that the occurrence of hypotension and body movement reactions was significantly lower in patients in groups B (0.05 mg/kg oxycodone) and C (0.1 mg/kg oxycodone) than in group A (0.025 mg/kg) and the control group (0 mg/kg groups) ($P < .05$). Therefore, we believe that the combination of 0.05 mg/kg oxycodone with propofol is a safe and effective anesthetic strategy for painless gastroscopic procedures. This is similar to the findings of Wang et al[27] who used different doses of oxycodone in combination with propofol for hysteroscopic procedures. We attribute this result to the good analgesic effect of oxycodone, which reduces the stress response of patients during painless gastroscopy.

The present study has several limitations. First, this study was a single-center study with a small number of subjects. A multicenter study with more subjects would be required to investigate the more accurate use of oxycodone in combination with propofol. In addition, the observation period of the study was relatively short and patient satisfaction was not assessed. Finally, the occurrence of side effects in this study was only assessed as a percentage and the severity of side effects was not further investigated.

In conclusion, 0.05 mg/kg oxycodone in combination with propofol can be used safely and effectively for painless gastroscopy, with the advantages of low propofol dosing, maintenance of hemodynamic stability and few adverse effects.

Author contributions

Data curation: Yan-Ping Li, Ying Zhou.
Funding acquisition: Ying Zhou.
Supervision: Yan-Ping Li.
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Writing – review & editing: Ying Zhou.

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