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Safety and efficacy of etomidate in combination with oxycodone in painless gastroscopic procedures in the elderly

A prospective randomized controlled trial study

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Abstract

Objective: Etomidate is often combined in rapid succession during induction of anesthesia. However, the effect of pretreatment with oxycodone on recovery of cognitive function and adverse effects has rarely been studied. We conducted a prospective randomized controlled trial to compare etomidate alone with etomidate combined with oxycodone in elderly patients undergoing painless gastroscopy.

Methods: Hundred elderly patients undergoing painless gastroscopy were divided into a control and an observation group, with 50 cases in each group. The age, gender, height, weight, body mass index and American Society of Anesthesiologists physical status (I/II) of patients in both groups were recorded. The recovery of cognitive function was compared in both groups using the Neurobehavioral Cognitive Status Examination. Adverse events, including somatic motor reactions, hypotension, bradycardia, myocardial tremor, nausea and vomiting, and injection pain, were also recorded in both groups. Moreover, heart rate, peripheral capillary oxygen saturation, systolic blood pressure, and diastolic blood pressure were evaluated in the 2 groups at different time points.

Results: A total of 100 patients were enrolled in this study. The demographic characteristics in the 2 groups were not significantly different ($P > .05$). Regarding the recovery of cognitive functions, more subjects in the observation group passed the memory, arithmetic and orientation test than in the control group ($P < .05$). Fewer adverse events such as dynamic body reactions, cardiac tremor, nausea and vomiting, and injection pain occurred in the observation group than in the control group ($P < .05$). During anesthesia and after awakening, the results of peripheral capillary oxygen saturation, systolic blood pressure and diastolic blood pressure were better in the observation group than in the control group ($P < .05$).

Conclusion: Etomidate in combination with oxycodone for painless gastroscopic operation in the elderly is a safe and effective anesthetic strategy.

Abbreviations: ASA = American Society of Anesthesiologists, BMI = body mass index, DBP = diastolic blood pressure, HR = heart rate, SBP = systolic blood pressure, SpO_2 = peripheral capillary oxygen saturation.

Keywords: adverse effects, anesthetic, etomidate, oxycodone, painless gastroscopy

1. Introduction

Gastroscopy is a commonly used technique in clinical practice for the diagnosis and treatment of gastrointestinal diseases.[1] It has several advantages, including clear visualization of lesions in the esophagus, stomach, and duodenum, easy collection of pathological biopsies, and local treatment.[1,2] However, the lens of the gastroscope must enter the gastrointestinal tract through the oropharynx during the procedure, which can easily cause pain, nausea and vomiting, and even asphyxia. Therefore, intravenous anesthesia is often used in painless gastroscopy to relieve the patient's discomfort and anxiety.[1]

Etomidate is a frequently utilized preoperative anesthetic for painless gastroscopic procedures. It has the advantage of rapid induction and low respiratory effects, but also the disadvantage of causing adverse effects such as myalgias, nausea, and vomiting due to inadequate analgesia.[3] Moreover, due to the poor general condition of elderly patients, most of them have combined respiratory and/or circulatory diseases, which increase the risk factors

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for the occurrence of adverse effects during painless gastroscopic procedures. Therefore, how to reduce the occurrence of adverse events, decrease patient pain and improve patient satisfaction during painless gastroscopic procedures in elderly patients is of great importance. Oxycodone is a novel semisynthetic opioid derived from the alkaloid thebaine.[4,5] It can agonize both μ- and κ-opioid receptors and has the advantages of rapid onset of action, better analgesia, and fewer adverse effects such as respiratory depression.[4,5] Oxycodone is an optional agent for the clinical management of acute pain,[6] chronic pain,[7] postoperative pain,[5,8] cancer-related pain,[9] visceral pain,[10] osteoarthritis-related pain,[5] and neuropathic pain.[10] Researchers believe it can be used as effectively as morphine in selected patients at the doses studied, with fewer side effects.[11]

Etomidate is often paired in rapid-sequence anesthesia induction. However, the effect of pretreatment with oxycodone on recovery of cognitive function and adverse effects during painless gastroscopy has been rarely investigated. Therefore, the primary aim of this study is to compare the effect of etomidate alone and etomidate in combination with oxycodone on cognitive function during painless gastroscopy in the elderly. Moreover, the secondary aim of this study was to compare the adverse events and vital signs of etomidate alone and etomidate in combination with oxycodone during painless gastroscopy.

2. Materials and Methods

2.1. Patient characteristics

This clinical trial was approved by the Medical Ethics Committee of the Third Hospital of Qinhuangdao City, Hebei Province, China (No. 2019-18). Patients and their families were informed about the study and signed the informed consent form. We selected 100 elderly patients who had undergone painless gastroscopy in the Third Hospital of Qinhuangdao, Hebei Province, China, from May 2016 to June 2021, and randomly divided them into a control and an observation group, with 50 cases in each group. The age, gender, height, weight, body mass index (BMI) and American Society of Anesthesiologists (ASA) physical status (I/II) of patients in both groups were recorded.

2.2. Inclusion and exclusion criteria

2.2..1. Inclusion criteria.

(1) Age ≥60 years;
(2) Patients with gastrointestinal diseases requiring painless gastroscopic procedures;
(3) All patients were classified as category I-II according to the ASA.

2.2..2. Exclusion criteria.

(1) Patients with an ASA classification more than III grade;
(2) Patients with a history of allergy to anesthetics or other drugs;
(3) Patients with mental illness and inability to cooperate with treatment.

2.3. Anesthesia technique

All patients were not allowed to eat food or drink water for 8 and 4 hours before gastroscopic surgery. After entering the room, the nasal catheter was inhaled with oxygen (3–5 L/minutes), and then the peripheral venous channel was opened. Subsequently, the patients' systolic blood pressure (SBP), diastolic blood pressure (DBP), heart rate (HR), and peripheral capillary oxygen saturation (SpO_2) were routinely monitored.

2.3..1. Control group.

Patients received an intravenous injection of sufentanil citrate (Sufentanil Citrate Injection, IDT Biologika CmbH, registration number H20100123) 1μg/kg, followed by a slow intravenous injection of etomidate (Etomidate Injection, Jiangsu Hengrui Pharmaceutical Co. H32022379) 0.15 mg/kg.

2.3..2. Observation group.

Patients received the same dose of sufentanil citrate as the control group. Oxycodone hydrochloride injection (NAPP PHARMACEUTICALS LIMITED, UK) 0.05 mg/kg was administered slowly intravenously for 2 minutes, and then etomidate injection 0.15 mg/kg was administered slowly intravenously.

After induction, the patient did not respond to verbal commands and the lash reflex disappeared. Gastrointestinal surgery could be performed immediately. All gastroscopic procedures were performed by the same clinically experienced physician. Patients were monitored during the procedure for body dynamic reactions, gag reflex, and HR. If abnormal body dynamics were noted, additional etomidate 0.05 to 0.1 mg/kg was administered to maintain anesthetic depth. If the patient's blood oxygen saturation was <90% during the examination, inhaled oxygen flow was increased and the patient's mandibular angle was supported. If the oxygen saturation had not improved, a breathing action can be performed by gently compressing the patient's chest and observing whether the patient's SpO_2 is elevated. If the SpO_2 was still below 90%, stop gastroscopy and quickly pull out the electronic gastroscope, hold up the mandibular back mask to support breathing, and perform gastroscopy after the SpO_2 is >90%. After the gastroscopy, the patient was taken to the observation room, attended by the nursing staff for anesthesia resuscitation, and left the operating room after 2 hours of wakefulness.

2.4. Assessment parameters

(1) Comparison of recovery of cognitive functions in the 2 groups using the Neurobehavioral Cognitive Status Examination.[12]
(2) The occurrence of adverse events, including somatic motor reactions, hypotension, bradycardia, myocardial tremor, injection pain, nausea, and vomiting, was recorded in both groups. In addition, nausea and vomiting due to side effects of the drug were not excluded in this study.
(3) We divided the whole anesthesia into 5 phases, namely "anesthesia induction time," "operation time," "recovery time," "orientation recovery time" and "departure time from the observation room," and then compared the duration of the different phases in the 2 groups.
(4) Comparison of the results of HR, SpO_2, SBP, and DBP in the 2 groups at different time points (before anesthesia, during anesthesia, and after waking up).

2.5. Statistical methods

SPSS software version 26.0 was used for the statistical analysis of the data. Measurement data was expressed as $\chi^2 \pm s$ and the t test was applied for comparison between groups; count data were expressed as frequency/rate (%), and the χ^2 test was applied for comparison between groups. $P < .05$ was considered a statistically significant difference.

3. Results

3.1. Demographic characteristics of the patients

A total of 100 patients were enrolled in this study. In the control group (n = 50), there were 33 males and 17 females; the mean age was 67.22 ± 7.22 years (from 60.00 to 74.44 years); the mean height was 173.21 ± 19.68 cm (from 153.53 cm to

192.82 cm); the mean weight was 75.63 ± 18.71 kg (from 56.92 kg to 94.34 kg); and mean BMI was 23.61 ± 1.24 (from 19.63 to 28.36). In the observation group (n = 50), there were 36 male and 14 female cases; the mean age was 66.56 ± 6.35 years (from 60.21 to 72.91 years); the mean height was 171.71 ± 16.92 cm (from 154.79 cm to 188.63 cm) the mean weight was 58.69 ± 15.31 kg (from 43.38 kg to 74 kg) and mean BMI was 23.07 ± 3.21 (from 19.86 to 26.28). There was no statistically significant difference between the general data of the 2 groups ($P > .05$). Besides, the number of patients with grade I/II of ASA physical status was also recorded (Table 1).

3.2. Recovery of cognitive functions

Regarding the recovery of attention, language ability, structural skills, and reasoning, the number of patients who passed the tests was similar in both groups, and the difference was not statistically significant ($P > .05$). However, for the memory, numeracy, and orientation tests, more individuals passed in the observation group than in the control group, and the differences were statistically significant ($P < .05$) (Table 2).

3.3. Occurrence of adverse events

Compared with the control group, fewer dynamic body reactions, myocardial tremor, nausea and vomiting, and injection pain occurred in the observation group, and the differences were statistically significant ($P < .05$). However, the differences in the occurrence of hypotension and bradycardia between the 2 groups were not statistically significant ($P > .05$) (Table 3).

3.4. Duration of the different anesthetic phases

The anesthesia induction time was 30.08 ± 6.71s in the observation group, which was significantly lower than 34.20 ± 9.11 in the control group ($P < .05$). However, gastroscopic surgery time was 26.15 ± 7.20 in the observation group, which was higher than 25.89 ± 8.24 in the control group, and the difference was not statistically significant ($P > .05$). In addition, compared to the control group, the observation group had a shorter wake-up time (21.10 ± 4.84 vs 26.01 ± 7.27), shorter recovery time from disorientation (22.98 ± 1.90 vs 29.97 ± 2.23) and shorter time to exit the observation room (26.63 ± 1.90 vs 33.54 ± 3.36) (all P values <.05) (Table 4).

Table 1

Characteristics of patients in the control group and observation group.

Characteristic	Control group (n = 50)	Observation group (n = 50)	P
Age (yr)	67.22 ± 7.22	66.56 ± 6.35	>.05
Height (cm)	173.21 ± 19.68	171.71 ± 16.92	>.05
Weight (kg)	75.63 ± 18.71	58.69 ± 15.31	>.05
BMI	23.61 ± 1.24	23.07 ± 3.21	>.05
Gender (male/female)	33/17	36/14	>.05
ASA physical status (I/II)	27/23	25/25	>.05

Values are presented as mean ± SD.
ASA = American Society of Anesthesiologists, BMI = body mass index.

Table 2

Comparison of cognitive recovery between the control group and the observation group.

Indicators	Control group (%)	Observation group (%)	P
Attention	43 (86.00)	44 (88.00)	.753
Memory ability	41 (82.00)	48 (96.00)	.006
Calculation ability	39 (78.00)	47 (94.00)	.006
Orienting ability	39 (78.00)	46 (92.00)	.026
Language ability	46 (92.00)	46 (92.00)	.631
Structural ability	48 (96.00)	49 (98.00)	.324
Deduction ability	45 (90.00)	46 (92.00)	.716

A P value <.05 means the difference is statistically significant.

3.5. Results of HR, SpO_2, SBP and DBP

The results of HR, SpO_2, SBP, and DBP were recorded before anesthesia, during anesthesia, and after awakening in the 2 groups. Before anesthesia, the differences in HR, SpO_2, SBP, and DBP between the 2 groups were not statistically significant ($P > .05$); during anesthesia, HR was higher in the observation group than in the control group; during anesthesia and after awakening, the results of SpO_2, SBP and DBP were better in the observation group than in the control group, and the differences were statistically significant ($P < .05$) (Table 5).

4. Discussion

Older adults usually have poor general physical health and are often burdened by other systemic diseases.[13] Gastroscopic procedures require the insertion of a tube, which can cause irritation of the pharynx, esophagus, and gastric mucosa.[14] Moreover, older people tend to feel tense, anxious, and fearful during this procedure, which also increases the occurrence of adverse events such as increased blood pressure and chest tightness.[15] Therefore, it is important to maintain hemodynamic stability in the elderly during the perioperative period of gastroscopic operation.

Etomidate is a short-acting intravenous anesthetic of the imidazole class, which has the advantages of rapid lipid-soluble metabolism and rapid onset of action, as well as low cardiovascular effects, no significant respiratory depression, and low sympathetic nerve effects, making it ideal for elderly patients.[1–3] However, the use of etomidate in high doses can suppress adrenocortical function and cause postoperative nausea, vomiting, myalgias, and other adverse effects.[2,3] It is essential to reduce the amount of etomidate and still achieve a satisfactory anesthetic effect for the elderly. Oxycodone has a potent analgesic effect and stimulates not only the μ receptor to suppress somatic pain but also the κ receptor to suppress visceral pain. During gastroscopic procedures, oxycodone can effectively suppress the injurious stimuli associated with the examination, but excessive amounts of oxycodone can cause respiratory depression.[4,6,8,11,16]

Postoperative cognitive dysfunction refers to changes in orientation, thinking, memory, attention, and other cognitive abilities in patients undergoing surgical anesthesia who have no preoperative psychiatric abnormalities.[17] The occurrence of postoperative cognitive dysfunction can impair recovery, prolong hospital stay and even affect the quality of life after discharge.[18,19] The elderly and the anesthesia technology are independent risk factors for the occurrence of postoperative cognitive dysfunction.[18] In this study, we used the Neurobehavioral Cognitive Status Examination method to compare the recovery of cognitive abilities in 2 groups of patients, and found that the observation group has more patients passed in the neurobehavioral cognitive tests than the control group, indicating that the combined application of oxycodone and etomidate accelerates postoperative cognitive recovery.

In the current study, the incidence of adverse effects including body-dynamic reactions, myalgias, nausea and vomiting, and injection pain was lower in the observation group than in

Table 3

Comparison of the occurrence of adverse effects between the control group and the observation group.

Adverse effects	Control group (%)	Observation group (%)	*P*
Body dynamic responses	17 (34.00)	4 (8.00)	<.05
Hypotension	3 (80.00)	1 (2.00)	>.05
Bradycardia	2 (6.00)	1 (2.00)	>.05
Myoclonus	24 (48.00)	0	<.05
Nausea and vomiting	18 (36.00)	4 (8.00)	<.05
Injection pain	48 (96.00)	1 (2.00)	<.05

A *P* value <.05 means the difference is statistically significant.

the control group. Thus, as far as the occurrence of side effects is concerned, etomidate in combination with oxycodone can relieve pain and reduce side effects, and the results of our study are consistent with previous studies.[20–22] An et al[21] described that oxycodone is effective for simultaneously preventing etomidate-induced myoclonus and rocuronium-induced withdrawal movements during general anesthesia induction.[21] Besides, Chao et al[23] reported that oxycodone along with etomidate can reduce the incidence of nausea and vomiting in painless cystoscopy. In our opinion, as oxycodone is the only μ- and κ-opioid receptor agonist in clinical practice, its combination with etomidate may compensate for the shortcomings of etomidate's incomplete analgesia. In addition, the use of oxycodone allows for a reduction in the dose of etomidate, which helps to avoid nausea and vomiting.

Two dosages of oxycodone, with 0.1 mg/kg and 0.05 mg/kg, have been mentioned in previous studies for pretreatment before anesthesia induction.[20,23,24] Considering the racial differences, we have used a more frequent dose in Asians, 0.05 mg/kg. In this study, the observation group had a shorter anesthesia induction time, wake-up time, and disorientation recovery time and left the observation room earlier than the control group, which was consistent with the results of Li et al.[24] In addition, the results of SpO_2, SBP, and DBP were better in the observation group than in the control group during anesthesia and after waking up. This suggests that etomidate in combination with oxycodone has a better anesthetic effect and can better maintain HR and blood pressure in elderly during gastroscopic procedures, which contributes to reducing the incidence of cardiovascular accidents. In our opinion, the main reason for this positive result is that oxycodone has a similar analgesic effect to morphine. Moreover, etomidate is a hypnotic intravenous anesthetic that does not affect respiratory function and can easily maintain cardiovascular stability and has no significant effect on HR during induction of anesthesia. Therefore, the combined use of the 2 anesthetics can play a synergistic analgesic and sedative role.[20,21]

Positive clinical results were obtained in this study. However, there are still some limitations that deserve our attention. First, this study did not investigate whether the combination of etomidate and oxycodone at different doses has an effect on anesthetic efficacy in elderly patients and needs to be further explored in clinical trials. Second, this study was conducted at a single center and a multicenter study with a large sample is still needed to assess the reliability of the results.

In conclusion, etomidate combined with oxycodone for painless gastroscopic surgery in the elderly is a safe and effective anesthetic strategy.

Author contributions

Data curation: Yan-Ping Li.
Methodology: Ying Zhou.
Writing – original draft: Ying Zhou.
Writing – review & editing: Yan-Ping Li.

Table 4

Comparison of the duration of different anesthesia phases between control and observation group.

Anesthesia phases	Control group (mean ± SD)	Observation group (mean ± SD)	*P*
Anesthesia induction time (s)	34.20 ± 9.11	30.08 ± 6.71	.045
Gastroscopic surgery time (min)	25.89 ± 8.24	26.15 ± 7.20	.684
Awakening time (min)	26.01 ± 7.27	21.10 ± 4.84	<.001
Time of orientation recovery (min)	29.97 ± 2.23	22.98 ± 1.90	<.001
Time to depart from observation room (min)	33.54 ± 3.36	26.63 ± 1.90	<.001

A *P* value <.05 means the difference is statistically significant.
SD = standard deviation.

Table 5

Comparison of HR, SpO_2, SBP and DBP between control and observation groups at different time.

	Before anesthesia			During anesthesia			After awakening		
Indicators	Control group (mean ± SD)	Observation group (mean ± SD)	*P*	Control group (mean ± SD)	Observation group (mean ± SD)	*P*	Control group (mean ± SD)	Observation group (mean ± SD)	*P*
HR (times/min)	72.41 ± 13.19	71.33 ± 13.27	>.05	68.57 ± 11.24	72.22 ± 13.01	<.05	68.27 ± 10.11	72.74 ± 11.03	>.05
SpO_2 (%)	95.17 ± 2.46	95.38 ± 2.21	>.05	93.43 ± 2.81	96.10 ± 3.67	>.05	93.02 ± 2.28	95.42 ± 3.13	<.05
SBP (mm Hg)	17.07 ± 2.41	17.11 ± 2.36	>.05	16.18 ± 2.01	17.42 ± 2.53	>.05	16.19 ± 2.16	17.42 ± 2.37	<.05
DBP (mm Hg)	7.54 ± 1.06	7.82 ± 1.18	>.05	7.06 ± 1.15	7.72 ± 1.33	>.05	7.25 ± 1.08	7.78 ± 1.31	<.05

A *P* value <.05 means the difference is statistically significant.
DBP = diastolic blood pressure, HR = heart rate, SBP = systolic blood pressure, SD = standard deviation, SpO_2 = peripheral capillary oxygen saturation.

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