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Original Article

Comparison of etomidate-remifentanil and propofol-remifentanil sedation in overweight or obese patients prior to diagnostic upper gastrointestinal endoscopy

Qian-Song Xiao[1*], Sheng-Tao Liao[2*], Yan-Hai Liu[1], Xing Ao[1], Ling Li[1], Ping Li[1], Dong-Feng Chen[1], Chun-Hui Lan[1]

[1]Department of Gastroenterology, Daping Hospital, Third Military Medical University, Chongqing 400042, China; [2]Department of Gastroenterology, The Second Affiliated Hospital of Chongqing Medical University, Chongqing 400010, China. [*]Equal contributors and co-first authors.

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Abstract: Objective: This study is to compare the hemodynamic responses, recovery and discharge times, diagnostic accuracy, patient and examiner satisfaction and adverse events of etomidate-remifentanil and propofol-remifentanil sedation in overweight or obese patients undergoing diagnostic gastroscopy. Methods: Three hundred overweight or obese patients (body mass index ≥ 25 kg/m^2) scheduled for diagnostic gastroscopy received intravenous etomidate-remifentanil (n = 150) or propofol-remifentanil sedation (n = 150), randomly. Remifentanil (0.4-0.6 μg/kg) was infused in all patients. Patients in the etomidate group received etomidate with an initial dose of 0.1-0.15 mg/kg followed by an additional dose of 4-6 mg/kg. Patients in the propofol group received propofol with an initial dose of 1-2 mg/kg and an additional dose of 20-40 mg/kg. The primary outcome was the Hemodynamic responses. The secondary outcomes included discharge times, diagnostic accuracy and patient and examiner satisfaction (The registration number: ChiCTR-TRC-13003162). Results: Etomidate-remifentanil caused less decreased levels of systolic blood pressure (SBP, $P < 0.01$), diastolic blood pressure (DBP, $P < 0.01$), SpO_2 ($P < 0.01$) and heart rate (HR, $P < 0.05$) than propofol-remifentanil. The onset time was earlier in the etomidate group ($P < 0.01$). Incidences of hypoxemia, hypotension and injection pain were higher in the propofol group (all $P < 0.01$), while those of myoclonus and nausea-vomiting were higher in the etomidate group (all $P < 0.01$). Satisfaction of physician and anesthetist in the propofol group was better. Conclusions: Etomidate-remifentanil sedation is feasible for overweight or obese patients undergoing gastroscopy.

Keywords: Gastroscopy, etomidate, propofol, overweight, obese, sedation

Introduction

Gastroscopy is a fundamental diagnostic and therapeutic method of upper gastrointestinal diseases. Although upper endoscopy is considered as a safe procedure, the morbidity and even mortality is still an issue [1]. Routine gastroscopy is frequently associated with adverse reactions as well as emotional responses which can reduce patients' tolerance and cooperation [2-4]. Reduction of several physiological functions, respiratory symptoms and a high incidence of cardiovascular diseases often occurs, particularly in overweight or obese patients [5, 6].

Overweight or obesity shows a limited quality of life and a high morbidity and mortality risk as a chronic disease [7]. Greater degrees of weight lead to more severe consequences for the respiratory system, cardiovascular system and other complications [5, 8-10]. Respiratory system compliance has been shown to be around 20% less in obese individuals compared to subjects who are of normal weight, and almost 60% less in patients with the obesity hypoventilation syndrome [11]. Besides, overweight is an important cardiovascular risk factor [12]. Some studies have reported higher HR in obese patients, compared to lean individuals [13].

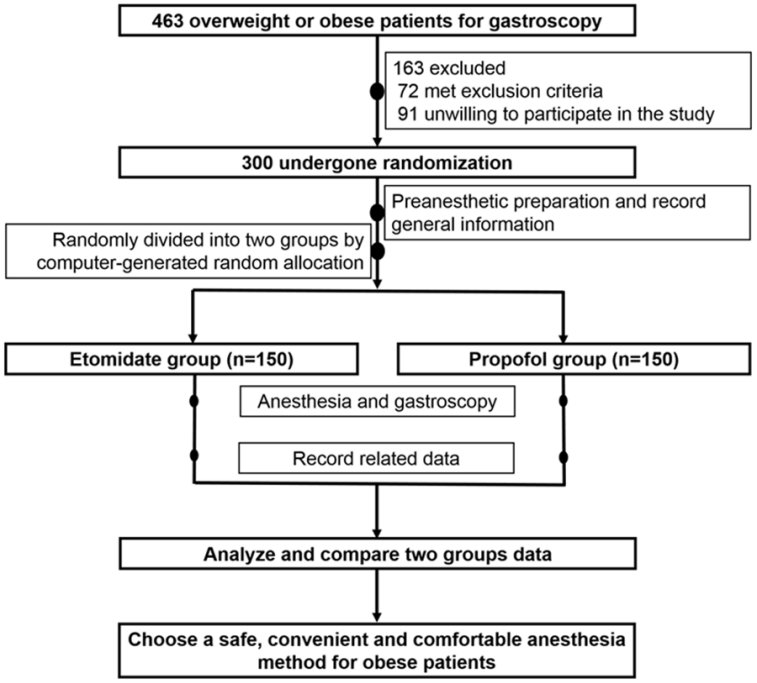

Figure 1. Flowchart of patient assignment for gastroscopy.

The administration of intravenous anesthesia during gastroscopy can relieve upper airway reflexes and improve the comfort of overweight or obese patients [14]. Quality management requires proper pharmacological training for all clinical staff involved in the practice of sedation, regardless of the type of sedation used [15]. Currently, Nonanesthesiologist-administered propofol (NAAP) is the direct administration of propofol by trained nurses or endoscopists and used regularly in many countries [16]. However, it may also lead to side effects common to deep sedation such as cough, dizziness, drowsiness, and cardiorespiratory distress including hypoxemia, hypotension, bradycardia, and dyspnea [2]. Cardiopulmonary complications account for more than 50% of all complications have much easier happen to the painless endoscopy [1, 17]. Moreover, overweight or obesity is a risk factor for cardiovascular disease and respiratory disease [5, 18, 19]. Overweight or obese patients undergoing gastroscopy have often underlying cardiopulmonary diseases predisposing to these complications [20-22]. They are more likely to happen to hypoxemia, hypotension, bradycardia, dyspnea, and arterial oxygen desaturation [23]. Etomidate has multiple pharmacologic effects that help facilitate sedation for endoscopy through interactions with the γ-aminobutyric acid (GABA) receptor. Etomidate clearance is reduced in the elderly, the obese, and those with hepatic or renal impairment. The major adverse effects are respiratory depression, apnea, and hypotension [24]. While propofol is a sedative-hypnotic drug with an amnestic effect, but a minimal analgesic effect. Major adverse effects are respiratory depression, hypotension, and pain on injection [25]. The effects of etomidate-remifentanil and propofol-remifentanil sedation used in overweight or obese patients are still unknown. We herein compared the effects of etomidate-remifentanil and propofol-remifentanil sedation in overweight or obese patients undergoing diagnostic gastroscopy.

Materials and methods

This is a single-center, prospective, and randomized study. The study protocol was approved by the Institutional Review Board at Daping Hospital, Third Military Medical University and was in accordance with the latest version of the Declaration of Helsinki for human experimentation (China Clinical Trial Registry No. ChiCTR-TRC-13003162). Written informed consent was obtained from each patient.

Patients

463 overweight or obese patients, aged 18-80 years, either sex, body mass index (BMI) ≥ 25 kg/m^2, American Society of Anesthesiologists (ASA) I-III and scheduled to diagnostic upper gastrointestinal endoscopy between March 2013 and July 2013 were included in this study. Exclusion criteria were patients with cardiac, pulmonary, hepatic or nephritic disease, metabolic disease, electrolyte disturbance, blood pressure > 180/110 mmHg, acute airway inflammation in the past two weeks, second degree atrioventricular block or complete left bundle branch block, or allergy to emulsion or opioid. Patients were randomly assigned into the etomidate-remifentanil group (n = 150) and the propofol-remifentanil group (n = 150) using a computer-generated simple random sampling

Table 1. Characteristics of patients undergoing gastroscopy with induction of anaesthesia using propofol-remifentanil or etomidate-remifentanil

	Propofol group (n = 150)	Etomidate group (n = 150)	*P*-value
Age (year)	43.67 ± 9.13	44.54 ± 10.02	0.22
Sex (M/F)	103/47	101/49	0.45
Body Mass Index	28.75 ± 2.48	28.53 ± 2.21	0.21
ASA physical status	1.93 ± 0.22	1.91 ± 0.34	0.27
Underlying medical conditions, n (%)			
Abnormal ECG	19 (12.67%)	20 (13.33%)	0.50
Hypertension	19 (12.67%)	17 (11.33%)	0.43
Allergy	2 (1.33%)	6 (4.00%)	0.14

Data are expressed as mean ± SD unless indicated otherwise. ASA, American Society of Anesthesiologists; F, female; M, male; ECG, Electrocardiograph.

technique. Assignment to the groups was determined by choosing the ordered number containing the labels propofol or etomidate which come from computer. Patients, endoscopists, and postoperative observers were blind to the group allocation (**Figure 1**).

Pre-procedure preparation and sedation

Prior to gastroscopic examination, all patients fasted from food and water for at least 6 hours, and then underwent 12-lead electrocardiography, routine blood tests, and coagulation tests. Venous access was performed with an indwelling needle. Intravenous 0.9% normal saline infusion was initiated in all patients. All patients were premedicated with 30 ml 0.5% oral dimethicone powder (Honghe Pharmaceutical Co., Ltd., Zigong, China) 30 min before gastroscopy, and with 10 ml viscous oral lidocaine hydrochloride (Kangye Pharmaceutical Co., Ltd., Handan, China) 15 min before gastroscopy.

Remifentanil (Yichang Humanwell, Hubei, China) was administered as 0.4-0.6 μg/kg intravenous infusions to all patients. Etomidate (Nhwa, Jiangsu, China) or propofol (AstraZeneca, Caponago, Italy) was administered after the remifentanil infusion started. Patients in the etomidate group received etomidate intravenously with an initial dose of 0.1-0.15 mg/kg followed by an additional dose of 4-6 mg/kg to maintain sedation. Patients in the propofol group received propofol with an initial dose of 1-2 mg/kg followed by an additional dose of 20-40 mg/kg.

Diagnostic upper gastrointestinal endoscopy

The gastroscopy was conducted after the eyelash reflex lost using a flexible electronic videoendoscope (EG-299-0i, Pentax, Tokyo, Japan). Two L/min oxygen was administered via a nasal cannula during the gastroscopy. Intravenous 0.9% normal saline infusion was initiated in all patients, then Hemodynamic parameters including systolic pressure, diastolic pressure, heart rate (HR), SpO_2 and Ramsay sedation score (RSS) were recorded. During gastroscopy, Hemodynamic parameters, HR, SpO_2 and RSS were recorded at 3-min intervals, then mean value of each index were calculated as the value during gastroscopy. After gastroscopy, Hemodynamic parameters, HR, SpO_2 and RSS were recorded again.

Recovery time which was evaluated as the period for which patients stayed in the recovery room until discharge and occurrences of hypoxemia, apnea, myoclonus, decrease of SpO_2 less than 95% or other adverse events were recorded during gastroscopy and before they left recovery room. The satisfaction of the physicians, anesthetists and overweight or obese patients was evaluated using a ten-point scale (1-4, poor; 5-7, fair; 8-10, good). Physicians and anesthetists' satisfaction refer to the procedure evaluation during gastroscopy. Patients were interviewed after full recovery to assess their satisfaction with the sedation.

Statistical analysis

Statistical analysis was performed by SPSS 13.0. Sample size analysis for detecting differences between groups was analyzed using a two-group t-test with a 5% two-sided significance level. All quantitative data were expressed as mean ± standard deviation (SD). All qualitative data were expressed as n (%) and compared using the chi-square test or Fisher's exact test. A *p*-value less than 0.05 was considered as statistically significant.

Table 2. Endoscopic diagnoses of patients with successful anaesthesia using propofol-remifentanil or etomidate-remifentanil

Symptoms	Propofol group (n = 150)	Etomidate group (n = 150)	*P*-value
Reflux esophagitis	9 (6.00%)	10 (6.67%)	0.50
Esophageal varices	0 (0.00%)	1 (0.67%)	0.50
Polyp	20 (13.33%)	18 (12.00%)	0.43
Hiatus hernia	2 (1.33%)	2 (1.33%)	0.69
Heterotopic Gastric Mucosa	8 (5.33%)	6 (4.00%)	0.39
Chronic nonatrophic gastritis	123 (82.00%)	118 (78.67%)	0.28
Chronic atrophic gastritis	26 (17.33%)	20 (13.33%)	0.21
Duodenitis	10 (6.67%)	13 (8.67%)	0.33
Peptic ulcer	17 (11.33%)	13 (8.67%)	0.28
Pre-or malignant disorders	2 (1.33%)	0 (0.00%)	0.25
Barrett's esophagus	16 (10.67%)	13 (8.67%)	0.35
Esophageal cancer	1 (0.67%)	0 (0.00%)	0.50
Gastric cancer	1 (0.67%)	0 (0.00%)	0.50
Low-grade intraepithelial neoplasia	5 (3.33%)	2 (1.33%)	0.22
Overall biopsy rate	42 (28.00%)	30 (20.00%)	0.07

Data are expressed as n (%).

Results

Patient characteristics and endoscopic outcomes

Patients in the two groups had no significant difference in age, sex, BMI, ASA physical status and underlying medical conditions (**Table 1**). The endoscopic diagnoses of overweight or obese patients were also comparable between the two groups, regarding the diagnoses of upper gastrointestinal benign or malignant diseases along the esophagus, stomach, and duodenum (**Table 2**).

Cardiorespiratory functions of patients before, during, and after the procedure

There were no significant difference in SBP, DBP, SpO_2, HR or Respiratory Rate (RR) between the two groups before gastroscopy. SBP, DBP, SpO_2, HR and RR change values according to the difference recorded before, during, and after the procedure are shown in **Figure 2**. SBP, DBP and SpO_2 decreased significantly than before gastroscopy between propofol group and etomidate group (22.48 ± 16.12 mm Hg versus 8.51 ± 17.19 mmHg, P < 0.01; 9.89 ± 12.69 mmHg vs 1.20 ± 12.87 mmHg, P < 0.01; and 2.53 ± 5.35% versus 0.53 ± 3.52%, P < 0.01, respectively), with both returning after gastroscopy (21.18 ± 15.87 mmHg versus 0.64 ± 15.87 mmHg, P < 0.01; 9.87 ± 11.73 mmHg vs -3.04 ± 12.09 mmHg, P < 0.01; and -0.67 ± 1.82% versus -0.76 ± 1.58%, P > 0.05, respectively). However, HR in the two groups was no significantly compared the difference before and during gastroscopy (-0.95 ± 10.78 cpm versus -1.22 ± 9.68 cpm, P > 0.05). And after the gastroscopy, change values increased to become significantly different before gastroscopy (1.52 ± 9.39 cpm versus -1.09 ± 10.13 cpm, P < 0.05). In two groups, no significant change was observed in RR before, during, and after the procedure (1.31 ± 5.14 cpm versus 2.22 ± 4.28 cpm, P > 0.05 and 1.89 ± 4.36 cpm versus2.23 ± 3.68 cpm, respectively).

Durations of endoscopy and satisfaction of physicians, anesthetists and patients

The duration time, recovery time and time to leave recovery room of two groups had no significant difference, whereas the onset time of the etomidate group was shorter (P < 0.01) compared with the propofol group (**Table 3**). The propofol group achieved better satisfaction feedbacks from both physicians and anesthetists (**Table 4**).

Endoscopic morbidities and complications

Adverse events were observed in both groups (**Table 5**). Generally, there were more patients having side effects in the propofol group than etomidate group (*P* < 0.01). Specifically, the hypoxemia, hypotension and injection pain had higher incidence in the propofol group (*P* < 0.01), while there was more myoclonus and nausea-vomiting occurred in the etomidate group (*P* < 0.01).

Discussion

We carried out etomidate-remifentanil and propofol-remifentanil sedation in overweight or

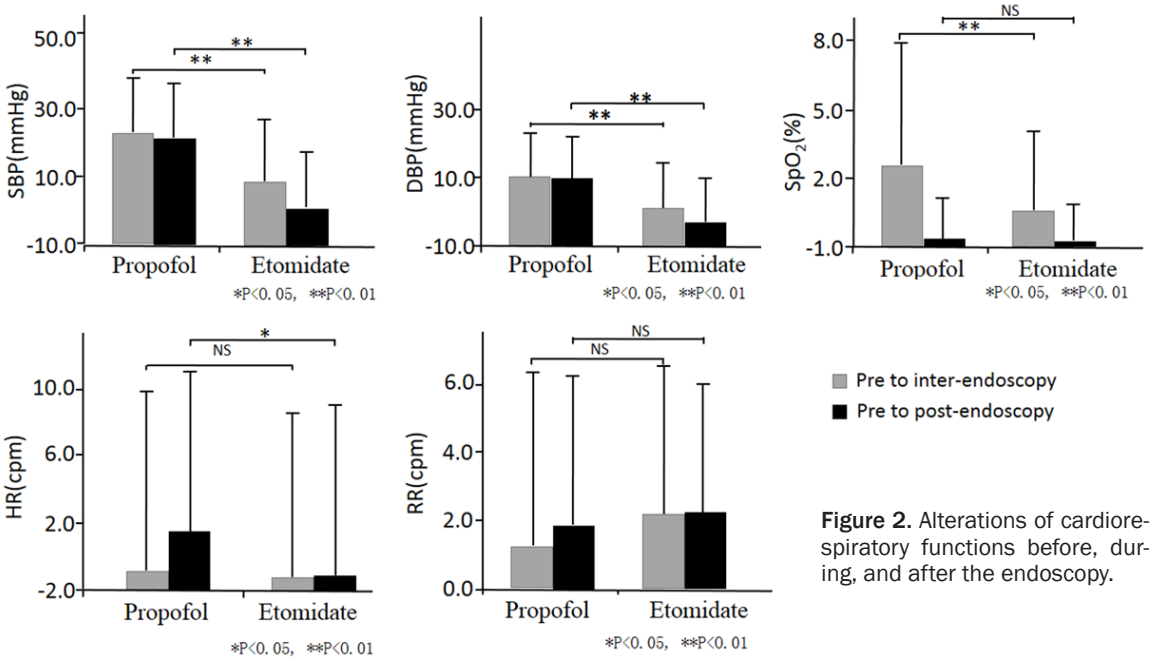

Figure 2. Alterations of cardiorespiratory functions before, during, and after the endoscopy.

Table 3. Mean drug doses, onset, duration, recovery and leave recovery room time values

	Propofol group (n = 150)	Etomidate group (n = 150)	*P*-value
Onset time (Sec)	83.68 ± 21.51	75.71 ± 12.07	< 0.01
Duration time (Sec)	292.41 ± 103.81	287.87 ± 120.83	0.36
Recovery time (Sec)	448.15 ± 138.82	470.97 ± 169.52	0.10
Time to leave recovery room (Sec)	945.63 ± 282.81	1021.21 ± 589.53	0.08

Data are expressed as mean ± SD.

obese patients scheduled to diagnostic upper gastrointestinal endoscopy. Hemodynamic responses, recovery and discharge times, diagnostic accuracy, patient and examiner satisfaction and adverse events were assessed. In this study, etomidate-remifentanil sedation is feasible for overweight or obese patients undergoing gastroscopy with less harmful effects, especially on cardiopulmonary function, hemodynamic responses and adverse events. Etomidate-remifentanil is also comparable to propofol-remifentanil regarding recovery and discharge times. In a similar study [26], They also reported that etomidate-remifentanil administration for sedation and analgesia resulted in more stable hemodynamic responses and shorter recovery and discharge times during colonoscopy. Compared with propofol-remifentanil sedation, etomidate-remifentanil sedation has no significant difference in diagnosis. Satisfaction of physician and anesthetist in propofol-remifentanil group was better, suggesting clinical etomidate-remifentanil infusion may need further improvement.

The overweight or obese patients receiving etomidate in this study had better haemodynamic performance than propofol during gastroscopy (**Figure 2**), suggesting etomidate has narrowed effects on hemodynamic stability and suppress blood circulation. It may be due to the advantage of etomidate in hemodynamic stability through the disadvantage of adrenocortical inhibition [27]. Propofol has been widely used as an anesthesia induction agent due to its enhanced depressant effects on the laryngeal reflexes [28]. But we observed its inhibitory effects on cardiovascular and respiratory function here, which may be due to peripheral vasodilator and inhibitive effects on cardiomyocytes. Wihelm et al. [29] has also proved mean arterial blood pressure and heart rate can decrease significantly after anesthesia induction with propofol. Propofol can also

Table 4. Examiner and patient satisfaction

	Propofol group (n = 150)			Etomidate group (n = 150)		
	Good	Fair	Poor	Good	Fair	Poor
Physician	147 (98.00%)	3 (2.00%)	0 (0.00%)	135 (90.00%)*	14 (9.33%)*	1 (0.67%)
Anesthetist	144 (96.00%)	6 (4.00%)	0 (0.00%)	132 (88.00%)*	18 (12.00%)*	0 (0.01%)
Patients	150 (100.00%)	0 (0.00%)	0 (0.00%)	149 (99.33%)	0 (0.00%)	1 (0.67%)

Data are expressed as n (%). *P < 0.05; Poor, 1-4; fair, 5-7; good, 8-10.

Table 5. Adverse events

Adverse events	Propofol group (n = 150)	Etomidate group (n = 150)	*P*-value
Yes	118 (78.67%)	69 (46.00%)	< 0.01
Upper airway obstruction	24 (16.00%)	23 (15.33%)	0.50
Hyoxemia	98 (65.33%)	61 (40.67%)	< 0.01
Apnoea	0 (0.00%)	0 (0.00%)	NA
Changes of heart rate and rhythm	2 (1.33%)	3 (2.00%)	0.50
Hypotension	42 (28.00%)	9 (6.00%)	< 0.01
Injection pain	20 (13.33%)	2 (1.33%)	< 0.01
Body quiver	3 (2.00%)	9 (6.00%)	0.07
Myoclonus	0 (0.00%)	12 (8.00%)	< 0.01
Nausea-vomiting	0 (0.00%)	10 (6.67%)	< 0.01
Deliration/Multilingual/Hallucination	0 (0.00%)	1 (0.67%)	0.50

Data are expressed as n (%). NA, Not applicable due to low event rate.

cause respiratory depression [30]. However, Recovery from propofol-induced respiratory depression was rapid [31]. Accordingly, we found SpO_2 in propofol group decreased significantly during gastroscopy but recovered rapidly. By contrast, etomidate seems to be an appropriate agent by offering hemodynamic stability for overweight or obese patients.

Adverse reactions were seen in both groups. Generally more adverse effects occurred in the propofol group than the etomidate group. A short-term sedation/analgesia study reported etomidate can cause less subclinical respiratory depression than propofol [32]. We found the hypoxemia, hypotension had higher incidence in the propofol group. Hypoxemia and hypotension is fatal for overweight or obese patients. Hypoxemia is closely related to SpO_2 and can be caused by propofol-induced sympathetic inhibition and disturbances in baroreflex mechanisms. However, etomidate preserves hemodynamic stability by stabilizing sympathetic responses and preserving autonomic reflexes [33], thus reducing the risk. There were twenty patients (13.33%) felt injection pain in the propofol group compared with two (1.33%) in the etomidate group. which is consistent with a previous study in children [34]. Lidocaine has been used to alleviate injection pain, which consequently complicates the operation procedure and leads to extra work. But here no lidocaine was administered because remifentanil pretreatment can relieve injection pain [35]. A frequent adverse event observed with etomidate is myoclonus [36]. The incidence of myoclonus has been estimated to be as high as 50-80%, especially if etomidate is used without pre-medication [37]. In this study, the incidence was 8.00% (12 patients) in the etomidate group compared with none in the propofol group. However, mild and short-lasting myoclonus did not impair the performance of the gastroscopy procedure. Nausea-vomiting is also common with etomidate. In this study ten patients (6.67%) had nausea-vomiting in the etomidate group, whereas none in the propofol group. However, nausea-vomiting were not severe and did not delay discharge.

Etomidate plays a neuroprotective role by reducing cerebral blood flow, intracranial pressure and cerebral oxygen metabolism. Patients in the etomidate group had a more rapid onset of action. But no significant difference else were seen in duration time, recovery time, and time to leave recovery room.

In a study examining the sedation levels of etomidate and propofol, the effects of the two drugs were found to be similar [38]. Propofol has been a preferred anesthetic agent. In order to choose a safe, convenient and comfortable

anesthesia method for overweight or obese patients undergoing a gastroscopy, we compared the effects of anesthesia induction by propofol-remifentanil and etomidate-remifentanil. We found etomidate also seems to be an appropriate agent for overweight or obese patients in clinical practice.

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Disclosure of conflict of interest

None.

Address correspondence to: Chun-Hui Lan, Department of Gastroenterology, Daping Hospital, Third Military Medical University, 10 Changjiang Branch Road, Chongqing 400042, China. Tel: +86-23-68757616; Fax: +86-23-68757616; E-mail: tiandaochouqin99@hotmail.com

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