

Effect of Etomidate on the Prevention of Propofol Injection Pain in Painless Endoscopy

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Abbreviations:

ASA: Anesthesiologists Classification; MAP: Mean arterial pressure; HR: Heart rate; NIBP: Non-invasive blood pressure; PI: Perfusion index; SD: Standard deviation

Keywords:

Etomidate; Propofol, Painless endoscopy; Injection pain

*Author Contribution:

Chen X, Tang Y and these authors are contributed equally to this work.

1. Abstract

1.1. Background: Propofol is one of the most commonly used short-acting sedatives for painless gastrointestinal endoscopy. Local injection pain during injection was the most common adverse effect. Therefore, this study intended to use a randomized controlled study to observe the effect of pre-etomidate on propofol injection pain by using a small amount of non-induced dose of etomidate. To study the preventive effect of etomidate on propofol injection pain in patients with painless endoscopy.

1.2. Methods: A total of Grade I-II American Society of Anesthesiologists Classification(ASA) 144 patients, who underwent painless gastrointestinal endoscopy in Fujian Provincial Hospital, were selected for the current study. Outpatients were divided randomly into two groups (n=72): the control group received a bolus injection of sufentanil (5 mg) + saline (3 mL) + propofol, and the etomidate group received a bolus injection of sufentanil (5 mg) + etomidate (6 mg) + propofol. The injection pain score was evaluated by Ambesh four-point scoring method, and the injection was stopped when the patient's consciousness disappeared. Also, the adverse reactions, such as respiratory and circulatory inhibition were observed.

1.3. Results: The grade of intravenous pain and the induction dose and total dosage of propofol were significantly lower in the etomidate group than those in the control group ($p < 0.001$). After induction, the lowest value of pulse oxygen saturation(SPO2) and mean arterial pressure(MAP) in the etomidate group and control group were lower

than that before induction ($p < 0.05$), and the rate of change in SPO2 and MAP in the etomidate group was significantly lower than that in the control group ($p < 0.05$).

1.4. Conclusion: The pre-injection of etomidate in painless endoscopic examination significantly reduces the pain of propofol-induced injection, the dose of propofol, and inhibition on the respiratory and circulatory system during painless endoscopic anesthesia.

2. Background

Gastrointestinal endoscopy is a non-traumatic invasive examination, which is widely used to screen gastrointestinal tumors and related diseases [1], and as a treatment for gastrointestinal bleeding, polyps, and foreign bodies [2]. Sedation was helpful to relieve preoperative anxiety and stress to reduce the complications [3], promote cooperation with doctors, and improve the success rate of endoscopy and patient satisfaction [4]. As one of the most commonly used short-acting sedatives for painless gastrointestinal endoscopy, propofol exhibited the advantages of safety, fast onset, less accumulation in a short time, and rapid recovery [5]. However, in adverse effects such as respiratory and circulatory inhibition [6], local injection pain during injection was the most common adverse effect and one of the factors limiting propofol application [7]. According to the reports, the occurrence rate of propofol injection pain was 28–90% [8], which could increase the patient's fear about the examination and have bad memories after the procedure.

Currently, the mechanism of propofol causing injection pain has not

been clear. It was been speculated [9] that injection pain of some narcotic drugs has a direct stimulatory effect caused by non-physiological osmotic concentration or high pH value. However, propofol is almost isotonic, not hyperosmotic, and has a pH of 6–8.5; therefore, this concept cannot explain the pain caused by propofol injection. It might be caused by the kinin cascade reaction by the action on venous endothelial tissue [10]. In addition, many factors could also cause injection pain, including the injection site, the speed of intravenous injection and infusion, the concentration of propofol in the water phase, and the blood buffering effect [11]. Hitherto, it was speculated that propofol injection pain could be divided into immediate injection pain and delayed injection pain (10–20 s after injection) [11]. At present, many methods, such as propofol injection in cubital fossa, pretreatment with lidocaine, opioid, and non-steroidal anti-inflammatory drugs, have been proposed to reduce injection pain. One of the most common method is lidocaine used solely as pretreatment or mixed with propofol [12]. Other drugs, including butorphanol, ondansetron, metoclopramide, and thiopental, were also applied [11]. Reportedly, injecting propofol into a large vein and cooling or heating propofol before injection could relieve the injection pain [13]. In practice, a variety of methods have been adopted for prevention. Although certain effects have been achieved, a satisfactory level is not yet achieved, with a pain occurrence rate of 32–48% [14]. These methods could not solve the psychological impact of pain during propofol injection [15], and hence, the adverse effects of these drugs should also be considered. Based on the use of propofol, this study tried to resolve the problem of the choice of drugs and methods to eliminate the propofol injection pain with easy operation and no additional adverse effects.

Etomidate is a short-acting intravenous hypnotic. Compared to propofol, it has the advantages of rapid onset, strong hypnotic effect, large safety margin, stable hemodynamics, mild respiratory inhibition [16], and causing forgetfulness. However, it had no effect on the heart rate and blood pressure but a mild dilation effect on the coronary blood vessels, which reduced its resistance and myocardial oxygen consumption, and did not significantly change myocardial contractility. It could be safely used in patients with acute cardiovascular instability risks [17]. Therefore, etomidate was often combined in clinical applications. Saricaoglu et al. conducted pharmacological studies and showed [18] that the combined use of propofol and etomidate reduced the dosage of propofol and stabilized the circulation and significantly reduced the occurrence rate of propofol injection pain, which could be attributed to the lipid solvent reducing the concentration of propofol. Thus, a decrease in bradykinin production and propofol concentration might be responsible for the reduced injection pain. Therefore, this study intended to use a randomized controlled study to observe the effect of pre-etomidate on propofol injection pain by using a small amount of non-induced dose of etomidate.

3. Methods

3.1. Clinical Data

This study was approved by the Ethics Review Committee of Fujian Provincial Hospital (ethics number: K2019-02-020) and registered at the China Clinical Trial Registration Center (www.chictr.org.cn), (Registration number: ChiCTR1900026561/Registration data: October 14, 2019), and all methods were performed in accordance with the relevant guidelines and regulations. Each patient signed the written informed consent, a total of 144 patients, who underwent painless gastrointestinal endoscopy in Fujian Provincial Hospital (Fuzhou, Fujian Province, China) from November 2019 to December 2019, were selected for the current study, regardless of gender, age 18–65-years-old, and grade I-II ASA. Exclusion criteria: patients who refused to participate in the study; patients allergic to propofol, fatty emulsion or etomidate; patients with severe cardiovascular, lung, liver, and kidney dysfunction; patients with obstructive sleep apnea hypopnea syndrome; patients with body mass index (BMI) ≥ 28 kg/m²; patients with a history of alcohol abuse or ingesting psychotropic drugs before surgery.

This study was a randomized double-blind controlled trial. Patients in the intervention group (etomidate group) received sufentanil (5 mg) + etomidate (6 mg) + propofol and those in the control group received sufentanil (5 mg) + saline (3 mL) + propofol; the occurrence rate of injection pain was the main observational indicator. According to the literature, the occurrence rate of propofol injection pain was estimated to be 75%, and that with etomidate intervention was 48%, while the standard deviation between propofol injection and etomidate intervention was 13.5%. The α was set as 0.05 (two-sided), power was 0.9, PASS 15 software was used to calculate the sample size of etomidate group (N1=64), and the sample size of control group (N2=64). Assuming that the loss to follow-up rate of the research subjects was 10%, the sample size, N1=72 cases and N2=72 cases, was required. The patients were randomly divided into two groups by the random number table method: the control group (n=72) and the etomidate group (n=72). The grouping scheme was placed in an opaque envelope, and the subjects and the pain assessment physician were not informed of the grouping scheme.

3.2. Anesthesia Method

After entering the preparation room, the venous access in the cephalic vein of all patients was established using No. 22 intravenous indwelling needle, and compound sodium chloride was dropped at the rate of 10 mL/kg/h (batch number: 190109 2N Anhui Shuanghe Pharmaceutical Co., Ltd, Wuhu, Anhui Province, China). After entering the examination room, Heart Rate (HR), Non-Invasive Blood Pressure (NIBP), pulse oxygen saturation (SPO₂), and Perfusion Index (PI) were monitored, and patients were facilitated oxygen inhalation through the nasal catheter at the rate of 4 L/min. The painless gastrointestinal endoscopy in both groups was performed by physicians with >10 years of operating experience. According to

the grouping situation of each patient in the envelope, the anesthesiologists administered a bolus injection of 5 mg sufentanil (batch number: Human well Sufentanil, Human well Pharmaceutical Co., Ltd, 1 mg/mL) + 3 mL normal saline (batch number: 190109 2N, Anhui Shuanghe Pharmaceutical Co., Ltd) + propofol (batch number: Lipofen, B. Braun Melsungen AG, Melsungen, Germany) to the control group and a bolus injection of 5 mg sufentanil + 6 mg etomidate (3 mL) (batch number: trade name: Forry, Jiangsu Nhwa Pharmaceutical Co., Ltd, National drug approval number H20020511) + propofol to the etomidate group. Each group was injected with propofol at a speed of 0.5 mL/s for anesthesia induction, and the target dose was 20–25 mg/kg until the patient's spontaneous breathing became slow and shallow and consciousness and eyelash reflexes disappeared; then, the endoscopic examination was performed immediately. From the beginning of the injection until the patient's consciousness disappeared, another anesthesiologist who was not aware of the grouping scheme used the Ambesh four-point scale [19] to score pain every 5–10 s according to the patient's main complaint and behavioral response: 0 point: no pain, no response to the inquiry; 1 point: mild pain, the patient had pain indication but no physical response; 2 points: moderate pain, the patient had pain indication and physical response; 3 points: severe pain, the patient had strong complaint of pain, accompanied by frowning, arm avoidance or tears, and other behaviors.

If the patient showed an involuntary position or insufficient sedation depth during the examination, 1–2 mL propofol was added in a single dose. The basic vital signs of the two groups of patients were maintained normal. If SPO₂ was <95% during the operation and the duration was longer than 30 s, the mandible was lifted up and the airway was opened, and it was defined as mild hypoxia. If SPO₂ was continuously lower than 90% for longer than 30 s, it was defined as severe hypoxia. Subsequently, the gastroscope catheter was removed, 100% pure oxygen was inhaled with mask, and balloon-assisted ventilation was performed. If HR was <50 beats/min, it was defined as bradycardia, and 2–3 mg anisodamine was injected intravenously. If SBP was <90 mmHg or the descend range was >30% of the base value, it was defined as hypotension and 2 mg dopamine was injected.

3.3. Observational Index

3.3.1. Main Index: Ambesh four-point pain scale; secondary observation index: induction dose and total dosage of propofol in the two groups, changes in HR, MAP, PI before and after anesthesia induction, the lowest value of SPO₂ after induction, and the adverse effects of each group. The total dosage of propofol was the sum of the induction dose and the supplemental dose. The adverse effects included mild or severe hypoxia, bradycardia, and hypotension. The time points of HR, MAP, and PI were recorded when consciousness disappeared during anesthesia induction.

4. Statistical Analysis

Excel 2016 was used for data entry and sorting, and the SPSS 17.0

statistical software (Nanjing Rbread Network Technology Co., Ltd, Nanjing, Jiangsu Province) was used for statistical processing. Categorical variables were expressed by the number of patients and percentages, and continuous variables with the normal distribution were expressed as mean ± standard deviation (SD). Categorical variables were analyzed by chi-square test, and continuous variables were analyzed by two-group independent sample t-test and two-factor repeated measure analysis of variance. The Bonferroni method was used for calibration. $p < 0.05$ indicated statistically significant difference.

5. Results

A total of 144 patients were included in this study. A total of 6 patients in the etomidate group were excluded due to refusal, and 3 patients in the control group were excluded due to the abandonment of gastrointestinal endoscopy. Finally, 66 patients in the etomidate group and 69 patients in the control group were analyzed (Figure 1).

- No statistically significant differences were detected in gender, ASA grading, age, height, weight, and BMI of patients between the two groups ($p > 0.05$), indicating that the baseline data of the two groups were similar (Table 1).
- The operation time and consciousness recovery time of the two groups of patients did not differ significantly, while the statistically significant differences were detected in pain grade, induction dose, total drug dose, and occurrence rate of adverse effects. The pain grade and the induction dose were significantly lower in the etomidate group than that in the control group ($p < 0.001$), while the total drug dose and the occurrence rate of adverse effects were significantly higher in the control group than those in the etomidate group ($p < 0.05$) (Table 2).
- Observation of vital signs before and after anesthesia induction in the two groups (Table 3)

5.1. Comparison of MAP Before and After Anesthesia Induction

According to the overall analysis, comparisons between groups did not show any significant difference in the MAP values between the two groups ($p > 0.05$), while intra-group comparison indicated statistically significant differences in the MAP values at each time point ($p < 0.001$). Also, an interaction effect was observed between the group and time point, which suggested that the MAP value was different at two time points and the rate of change between the two time points was different. Pairwise comparison showed that the MAP value after induction was lower than that before induction, and the change in the MAP value before and after induction in the control group was higher than that in the etomidate group ($p < 0.005$), indicating that MAP value decreased after induction than before induction, and the rate of change of MAP value in the etomidate group was slower than that in the control group.

Table 1: Comparison of baseline information of the two groups

Index		Control group (n=69)	Etomidate group (n=66)	p-value
Gender	Male	40	29	0.103
	Female	29	37	
ASA grading	1	37	35	0.945
	2	32	31	
Age (years)		48.65±12.03	51.08±10.72	0.219
BMI		23.02±2.70	23.16±2.76	0.763

Note: BMI = Weight (kg) / height (m)²

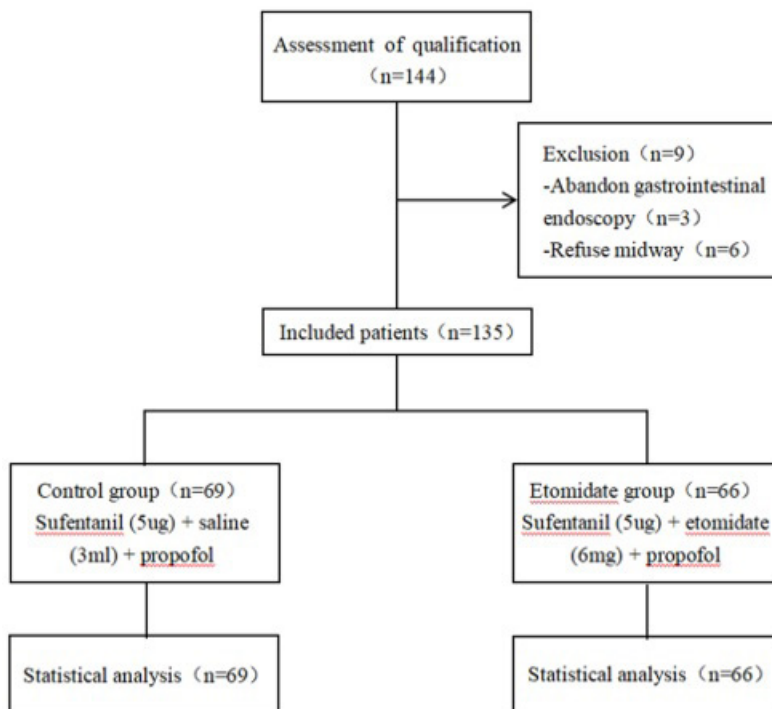
Table 2: Comparison of different indicators between the two groups

Index		Control group (n=69)	Etomidate group (n=66)	p-value
Induction dosage		12.71±3.31	9.02±2.47	<0.001
Total dosage (mL)		23.67±7.03	18.09±7.24	<0.001
Operation time (min)		18.01±7.04	17.92±6.77	0.94
Consciousness recovery time(sec)		20.36±7.37	18.80±6.96	0.209
Adverse effects	None	52	59	0.033
	Mild hypoxia	5	3	
	Severe hypoxia	2	0	
	Bradycardia	4	2	
	Hypotension	5	2	
Pain grading	0	39	65	<0.001
	1	22	1	
	2	6	0	
	3	2	0	

Table 3: Changes of vital signs before and after induction in the two groups

Group	Time	HR (bpm)	MAP (mmHg)	PI	SPO ₂ (%)	
Control	Before induction	79.01±12.55	98.12±12.01	3.34±2.46	98.06±1.69	
	After induction	69.62±8.02	77.86±10.25	7.39±3.76	95.86±5.24	
Experimental	Before induction	79.35±10.76	97.70±15.14	3.64±2.38	97.89±1.97	
	After induction	69.64±9.18	82.50±14.24	7.62±3.83	97.73±3.13	
Comparison between groups		F,p ^a	0.012,0.913	1.080,0.301	0.335,0.564	3.879,0.051
Comparison before and after induction		F,p ^b	145.955,<0.001	354.903,<0.001	201.586,<0.001	10.011,0.002
Interaction effect		F,p	0.041,0.840	7.239,0.008	0.016,0.898	7.393,0.007

Note: A indicated the comparison between the control and experimental groups at the same time point; b indicated the comparison before and after induction in the same group.

**Figure 1:** Flowchart of inclusion and exclusion criteria

5.2. Comparison of PI Before and After Anesthesia Induction

According to the overall analysis, comparisons between groups revealed statistically significant differences in the PI values between the two groups ($p > 0.05$), and intra-group comparison indicated statistically significant differences in the PI values at each time point ($p < 0.001$). However, there was no interaction effect between the group and time point, which could be attributed to the different PI values at two time points. Pairwise comparison showed that the PI value before induction was lower than that after induction, indicating that the PI value increased after induction than before induction.

5.3. Comparison of SPO2 Before and After Anesthesia Induction

According to the overall analysis, comparisons between groups demonstrated statistically significant differences in SPO2 values between the two groups ($p > 0.05$). Intra-group comparison indicated statistically significant differences in the SPO2 values at each time point ($p < 0.05$). Simultaneously, an interaction effect was detected between the group and time point, and hence, could be considered that the SPO2 value was different at two time points and the rate of change between the two time points was different. Pairwise comparison showed that the SPO2 value after induction was lower than that before induction, the change in the SPO2 value before and after induction in the control group was higher than that in the etomidate group ($p < 0.05$), indicating that SPO2 value decreased after induction than before induction, and the rate of change in the SPO2 value in the etomidate group was slower than that in the control group.

6. Discussion

In this study, we found that pre-injection of etomidate was effective in reducing the occurrence rate and severity of propofol injection pain with less propofol dosage and less effect on respiration and hemodynamics.

In this study, the occurrence rate of intravenous pain in the etomidate group (1.52%) was significantly lower than that in the control group (43.48%). According to the results of the pain intensity rating, the grade of intravenous pain in the etomidate group was significantly lower than that in the control group, which was consistent with our hypothesis, indicating that etomidate pre-injection could prevent the intravenous pain caused by propofol in painless endoscopy.

In addition, the results showed that the induction and total dosages of the etomidate group were significantly lower than those of the control group, indicating that etomidate pre-injection could reduce the dosage of propofol. MAP and SPO2 decreased after induction as compared to that before induction in both groups, and the change in the rates of MAP and SPO2 in the etomidate group was lower than those in the control group, indicating that etomidate pre-injection group had a milder effect on the respiration and circulation. The occurrence rate of adverse effects in the control group was higher than that in the etomidate group, indicating that the occurrence rate

of adverse effects in the etomidate pre-injection group was lower and the safety was higher.

The injection pain caused by propofol could be divided into immediate injection pain and delayed injection pain. Propofol, as a phenolic compound, could stimulate blood vessels and mucous membranes, resulting in pain. The immediate injection pain was related to the contact of propofol free in the water phase with the inner wall of the blood vessel, which directly stimulated the vascular endothelium and might be related to the concentration of free propofol in the aqueous solution [20]. Previous studies speculated that the mechanism of delaying pain was that propofol acted on venous endothelial tissue, which stimulated the kallikrein-kinin system to produce bradykinin, dilated the blood vessels and increased the vascular permeability, and establishing the contact of free propofol with the nerve endings of the inner wall of the blood vessels that caused pain [21]. Some studies have shown that injection pain was related to prostaglandins, especially prostaglandin E2 [21]. Typically, factors associated with the injection pain included: concentration of free propofol in aqueous solution, preparation type, grease solvent, injection technique (injection site, injection speed, intravenous infusion, puncture technique, and syringe material), blood buffering, filtration treatment, and age [22].

In this study, the pre-injection of etomidate prevented and alleviated the propofol injection pain, considering the following reasons: 1. The molecular weight, structure, and excipients of etomidate and propofol were different, and the two drugs had different occurrence rate of pain at the injection site. Because etomidate had a low occurrence rate of intravenous injection pain, when etomidate was pre-injected, various components of the drug could adhere to vascular endothelial tissues in advance, thus cushioning the subsequent pain effect on the vascular wall tissues. 2. The proportion of fat emulsion in etomidate was different. During pre-injection, the propofol in the free water phase was further wrapped by the fat emulsion in etomidate, which reduced the concentration of propofol in the free aqueous phase of blood vessels, reduced the stimulating effect of free propofol on the inner wall of blood vessels, and reduced the release of bradykinin, thereby reducing the possibility of immediate pain caused by propofol directly stimulating the vascular endothelium. 3. Pre-administration of 5 mg sufentanil plus 6 mg etomidate placed the patient under sub-anesthetic state in advance, reducing the sensitivity of the central system to peripheral pain and thus, alleviating or preventing the intravenous injection pain.

Propofol was a powerful cardiovascular inhibitor with antihypertensive adverse effects, which might cause serious consequences [21]. On the other hand, propofol used for sedation causes other potential adverse events, such as apnea and decreased SPO2 [22]. High dose or rapid infusion of propofol reduces respiratory frequency and tidal volume [23], which might eventually lead to hypoxia. These adverse effects are closely related to the dose and speed of propofol injection

[24]. Another study reported [25] that compared to propofol used solely, the combination of propofol and etomidate improves the hemodynamic stability of patients, who underwent endoscopy and reduced the dosage of propofol, which was consistent with our observation. This phenomenon could be attributed to the sedative effect of etomidate, and propofol combined with etomidate to achieve the required sedation depth could reduce the induced amount of propofol, thereby improving the hemodynamic stability and reducing respiratory depression of patients undergoing endoscopy. Consistent with this study, etomidate had unique properties that allowed its usage in combination with propofol for anesthesia in patients undergoing endoscopy. The results of meta-analysis showed that [26] the combination of etomidate and propofol significantly reduced the occurrence rate of muscle tremor caused by etomidate [27]. The pre-treatment with neuromuscular blockers, dexmedetomidine, opioids, low-dose ketamine, midazolam, dezocine, gabapentin, and magnesium sulfate could prevent etomidate-related muscle tremor; however, these drugs had adverse effects such as delayed recovery, excessive sedation, and respiratory inhibition [28]. However, in this study, etomidate group was given a small amount of etomidate (6 mg), which did not reach the anesthetic dose, avoided the complications of body movement and muscle tremor caused by single overdose and greatly reduced the adverse effects caused by etomidate. Intriguingly, both groups used a small amount of sufentanil (5 mg) to control stress and further reduced the adverse effects caused by etomidate. On the other hand, the etomidate group was given propofol immediately after etomidate achieved the required anesthetic depth. Previous studies [25] also showed that propofol could prevent or alleviate the muscle tremor caused by etomidate induction. Furthermore, the frequency of mild hypoxia and severe hypoxia in the control group was slightly higher than that in the etomidate group, albeit not significant, which could be investigated by increasing the sample size in future experiments.

Nevertheless, the present study has some limitations: 1. The number of patients included was relatively small; 2. The grade of injection pain was assessed by Ambesh four-point scale, which was personal subjective feeling, the subjective feeling of the subjects was determined by their personal characteristics. In addition, after a bolus injection of sufentanil (5 mg) + etomidate (6 mg), the patient quickly entered the sedative state, and hence, there was no response to the inquiry. 3. Adrenal function was not assessed after sedation. Etomidate reduces adrenal function; however, but this was usually transient and would not increase mortality. Notably, a large number of samples could be assessed in the future, and an improved pain evaluation system could be formed. Moreover, the specific internal mechanism of propofol pain could be detected, in order to reduce the occurrence rate and degree of propofol injection pain and provide patients with comfortable and painless anesthesia and surgical procedures.

7. Conclusions

Pre-injection of etomidate reduces the occurrence rate and severity of propofol injection pain in patients undergoing gastrointestinal

endoscopy. This in turn reduces the dosage of propofol and the inhibition of respiration and circulation during anesthesia, and is safe, thereby deeming it optimal for clinical application.

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