Research Paper

# Etomidate Anesthesia during ERCP Caused More Stable Haemodynamic Responses Compared with Propofol: A Randomized Clinical Trial

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## Abstract

**Background:** Propofol may result in hypotension and respiratory depression, while etomidate is considered to be a safe induction agent for haemodynamically unstable patients because of its low risk of hypotension. We hypothesized that etomidate anesthesia during ERCP caused more stable haemodynamic responses compared with propofol. The primary endpoint was to compare the haemodynamic effects of etomidate vs. propofol in ERCP cases. The secondary endpoint was overall survival.

**Methods:** A total of 80 patients undergoing ERCP were randomly assigned to an etomidate or propofol group. Patients in the etomidate group received etomidate induction and maintenance during ERCP, and patients in the propofol group received propofol induction and maintenance. Cardiovascular parameters and procedure-related time were measured and recorded during ERCP.

**Results:** The average percent change to baseline in MBP was -8.4±7.8 and -14.4±9.4 with $P = 0.002$, and in HR was 1.8±16.6 and 2.4±16.3 with $P = 0.874$ in the etomidate group and the propofol group, respectively. MBP values in the etomidate group decreased significantly less than those in the propofol group ($P < 0.05$). The ERCP duration and recovery time in both groups was similar. There was no significant difference in the survival rates between groups ($p = 0.942$).

**Conclusions:** Etomidate anesthesia during ERCP caused more stable haemodynamic responses compared with propofol.

Key words: Etomidate anesthesia, propofol

## Introduction

Over the last few years, there has been growing interest in the use of propofol in endoscopic procedures. However, propofol may result in hypotension, respiratory depression, and loss of protective reflexes. It is extremely important to ensure the patient's clinical stability during endoscopic procedures.[1] Most patients who need ERCP suffer from obstructive jaundice. Patients with obstructive jaundice are prone to develop hypotension and bradycardia during anesthesia induction and maintenance compared with nonjaundiced patients.[2-4] Etomidate is a nonbarbiturate hypnotic that induces anesthesia through GABA receptors in the central nervous system.[5] Etomidate is considered to be a safe induction agent for haemodynamically unstable patients because of its low risk of hypotension.[6, 7] Etomidate for proce-

dural sedation has been used in emergency departments for many years.[8-10] Recently, it was reported that etomidate for sedation during colonoscopy resulted in more stable haemodynamic responses and shorter recovery and discharge times compared with propofol.[11] However, there are some conflicting results on the adverse effect of etomidate on adrenocortical suppression. One recent paper compared much larger numbers of patients given etomidate and propofol, and found that etomidate was associated with an increased risk of 30-day mortality, cardiovascular morbidity, and prolonged hospital stay [12], while another systematic review showed that etomidate suppressed adrenal function transiently without demonstrating a significant effect on mortality.[13]

In the present study, we hypothesized that etomidate anesthesia during ERCP causes more stable haemodynamic responses compared with propofol. The primary endpoint was to compare the haemodynamic effects of etomidate vs. propofol in ERCP cases. The secondary endpoint was overall survival. Overall survival was defined as the interval between treatment and death of any cause.

## Methods

This study was approved by the Committee on Ethics of Biomedicine Research, Eastern Hepatobiliary Surgery Hospital (EHBHKY-2013-002-003) prior to its start. The registration number of randomized clinical trials is ChiCTR-TRC-13003850 (The URL is http://www.chictr.org/cn/. The name of the principal investigator is Jinchao Song). A total of 80 ASA I-III patients undergoing ERCP, aged 18-70 years and weighing 45-90 kg, were enrolled in this study. Written consent was obtained from all subjects. Patients with known adrenocortical insufficiency, chronic sedative or opioid analgesic use, known allergy to the study drugs, heart failure (ejection fraction <40%), and/or severe respiratory disease (vital capacity and/or forced expiratory volume <50%) preoperatively were excluded from this study. The patients were computer-randomized into either the etomidate group or the propofol group. The patients, gastroenterologists, anesthesiologist assistant and nurses in the recovery room were blinded to the grouping. The anesthesiologist assistant observed and recorded vital signs through a local area network in the next room.

All patients were premedicated with an intramuscular injection of 100mg pethidine twenty minutes before entering the endoscopy room. BIS (BIS™ XP sensor), noninvasive blood pressure, heart rate (HR), ECG and peripheral oxygen saturation (SpO$_2$) were monitored continuously throughout the study in the endoscopy room (Philips HP Viridia 24/26 M1205A). A 20-gauge intravenous cannula was placed in the peripheral vein for 0.9% normal saline infusion and drugs. The BIS sensor (BIS™ XP) was applied according to the manufacturer's recommendations. Oxygen was administered at a rate of 5 L/min by nasal catheter during ERCP. All the patients underwent ERCP in the prone position without tracheal intubation. After recovery, 50-100mg of pethidine was given, if necessary.

Baseline values of mean arterial blood pressure (MBP) were measured at 5 minutes after the patient entered the endoscopy room. Then, all patients received 2-2.5 mg midazolam (IV). After 5 minutes, induction was started. In the etomidate group, etomidate was delivered at a rate of 30 µg•kg$^{-1}$•min$^{-1}$ by a Graseby 3500 syringe pump (SIMS Graseby Ltd., Herts, England) until the BIS was 50, then ERCP was started. Anesthesia was maintained with etomidate (8-12 µg•kg$^{-1}$•min$^{-1}$) during ERCP. In the propofol group, propofol was delivered at a rate of 0.3 mg•kg$^{-1}$•min$^{-1}$ until the BIS was 50, and anesthesia was maintained with propofol (0.12-0.18 mg•kg$^{-1}$•min$^{-1}$). BIS was used to monitor the depth of anesthesia during the ERCP operation, and controlled at about 50 by fine-adjusting anesthetic agents. Emergency equipment was available throughout the ERCP procedure. Dopamine (2-5 µg • kg$^{-1}$ • min$^{-1}$) or an appropriate dose of metaraminol was given once MBP fell below 60 mmHg, and 0.25mg atropine was given once HR fell below 50 bpm. Appropriate nitroglycerin was given once MBP rose above 120 mmHg, and appropriate esmolol was given once HR rose above 120 bpm. If spontaneous ventilation was insufficient (SpO$_2$ < 92%), the anesthesiologist performed assisted mask ventilation as necessary. If myoclonus was observed in the etomidate group, 50-100mg propofol was given and propofol took the place of etomidate in anesthesia maintenance. ERCP procedures were performed in a standardized manner under the supervision of two experienced gastroenterologists.

MBP, HR, SpO$_2$ were measured and recorded at the designated time points: T$_0$ = baseline values, 5 min after entering the endoscopy room; T$_1$ = 5 min after the patients received midazolam; T$_2$= when BIS was 50 (after induction of etomidate or propofol); T$_3$ = at scope intubation and T$_{4-10}$ = by 5-min intervals during the ERCP. The induction time, duration of ERCP and recovery time were recorded.

The patient's satisfaction with the procedure (1 = unacceptable, 2 = extremely uncomfortable, 3 = slightly uncomfortable, 4 = no discomfort) was assessed 1 hour after ERCP. The gastroenterologist's satisfaction was assessed immediately after ERCP as: 1, poor; 2, fair; 3, good; 4, excellent.[14]

Clinical signs of adrenocortical suppression such

as hypotension and arrhythmia were monitored carefully after ERCP since etomidate may transiently cause adrenal suppression. After ruling out the general reason of hypotension and arrhythmia, we may consider adrenocortical suppression in etomidate group. Hydrocortisone (200-300 mg per day) was given if necessary.

The primary endpoint was the average percent change to baseline in mean arterial pressure and heart rate. Percent change = $(MBP_{T1-10} - MBP_{T0})/ MBP_{T0} * 100$. The secondary endpoint was overall survival. Overall survival was defined as the interval between treatment and death of any cause.

The group sample size was calculated based on the result of a pilot study, in which we found that the average percent change to baseline in mean arterial pressure was -7.5±8.3 (n = 12) in the etomidate group and -13.5±10.3 (n = 12) in the propofol group. 38 samples for each group met the requirement of α = 0.05 and power = 0.8.[15]

All data in the text and tables are expressed as mean±SD, number (n) or percentage. Continuous outcomes with normal distribution were analyzed with independent 2-sample t-test. The count data were compared using the χ2 test or Fisher's exact test or Continuity correction where appropriate. Reported *P* value was 2-sided, with $P < 0.05$ considered statistically significant. The Kaplan-Meier estimate was used in survival analysis. All analyses were conducted using SPSS 17.0 (SPSS Inc., Chicago, IL). Figures were made using GraphPad Prism 5.

## Results

The study was completed without any significant clinical complication. There was no statistical significance between characteristics of patients such as gender, age, body height, weight or diagnosis (Table 1).

The average percent change to baseline MBP was -8.4±7.8 and -14.4±9.4 with *P* = 0.002, and average percent change to baseline HR was 1.8±16.6 and 2.4±16.3 with *P* = 0.874 in the etomidate group and the propofol group, respectively. MBP values in the etomidate group decreased significantly less than those in the propofol group ($P < 0.05$). Figure 1, 2 shows the time course of percent change to baseline in mean arterial pressure and heart rate. Figure 3 shows the $SpO_2\%$ levels over the designated time points.

Induction time was longer in the etomidate group (P<0.05), but there was no statistical significance between groups for ERCP duration and recovery time (P>0.05) (Table 2). There was no statistical significance between groups for patient satisfaction and gastroenterologist satisfaction (P>0.05) (Table 2). The mean hospital stay was 8.7 days in the etomidate

group *vs.* 8.6 days in the propofol group (n.s.).

All adverse events during and after ERCP are presented in Table 3. There was significantly more injection site pain in the propofol group ($P < 0.05$).

There was no significant difference in the survival rates between groups ( *p* = 0.942).

**Table 1.** Patient Characteristics and Pre-operative Laboratory Values.

|  | Etomidate group (n=40) | Propofol group (n=40) | *P* |
|---|---|---|---|
| Gender, M/F | 28/12 | 28/12 | - |
| Age, yr | 55.8±10.6 | 52.4±11.4 | 0.172 |
| Body height, cm | 164.8±8.6 | 164.1±8.3 | 0.762 |
| Weight, kg | 62.4±11.4 | 63.5±11.8 | 0.709 |
| Bilirubin, μmol/L | 118.2±117.8 | 108.2±142.2 | 0.748 |
| WBC, ×10⁹/L | 5.2±1.7 | 5.9±2.0 | 0.126 |
| ASA ( I / II /III) | 18/15/7 | 17/16/7 | - |
| Benign disease, n | 22 | 23 | - |
| Malign disease, n | 18 | 17 | - |

Data are expressed as Mean±SD or number of patients. ASA, American Society of Anesthesiologists. Malign disease includes mainly Carcinoma of head of pancreas, Gallbladder Carcinoma, Hilar bile duct cholangiocarcinomas, Carcinoma in the middle and distal bile duct, and Intrahepatic bile duct cholangiocarcinomas. Benign disease includes mainly Intrahepatic bile duct stone, Choledocholithiasis, and Common bile duct stricture.

**Table 2.** Procedure-related time, satisfaction. and hospital stay

|  | Etomidate group (n = 40) | Propofol group (n = 40) | *P* |
|---|---|---|---|
| Induction time (min) | 5.6±0.8 | 5.2±0.9 | **0.037** |
| Duration of ERCP (min) | 20.9±8.4 | 20.4±9.2 | 0.800 |
| Recovery time (min) | 14.5±9.3 | 15.2±6.1 | 0.702 |
| Patient satisfaction | 3.8±0.4 | 3.8±0.3 | 0.419 |
| Gastroenterologist satisfaction | 3.8±0.4 | 3.8±0.4 | 1.000 |
| Hospital stay (days) | 8.7±3.6 | 8.6±3.3 | 0.856 |

Data are expressed as Mean±SD. Induction time (the time from starting propofol/etomidate to BIS = 50), Duration of ERCP (the time from scope intubation to scope withdrawal), and Recovery time (the time from stopping the drugs to full recovery (modified Aldrete score of 10)).

**Table 3.** Adverse events

|  |  | Etomidate group n (%) | Propofol group n (%) | *P* |
|---|---|---|---|---|
| During ERCP | Desaturation | 0 | 0 | - |
|  | Apnoea | 0 | 0 | - |
|  | Hypotension | 1 (2.5) | 1 (2.5) | 1.000 |
|  | Bradycardia | 0 | 0 | - |
|  | Hypertension | 2 (5) | 1 (2.5) | 1.000 |
|  | Tachycardias | 4 (10) | 6 (15) | 0.499 |
|  | Nausea-vomiting | 1 (2.5) | 1 (2.5) | 1.000 |
|  | Myoclonus | 1 (2.5) | 0 | 1.000 |
|  | Injection site pain | 0 | 6 (15) | **0.034** |
| After ERCP | Pancreatitis | 0 | 0 | - |
|  | Cholangitis | 1 (2.5) | 2 (5) | 1.000 |
|  | Sepsis | 0 | 0 | - |
|  | Adrenal crisis | 0 | 0 | - |

Data are expressed as percentage. Desaturation (oxygen saturation <90% for >10 seconds); Apnoea (cessation of respiratory activity for over 10 seconds); Hypotension (MBP < 60 mmHg or decreases more than 25% from the baseline); Bradycardia (HR <50 bpm); Tachycardias was defined as HR >120 bpm in this study. Hypertension was defined as MBP > 120 mmHg.
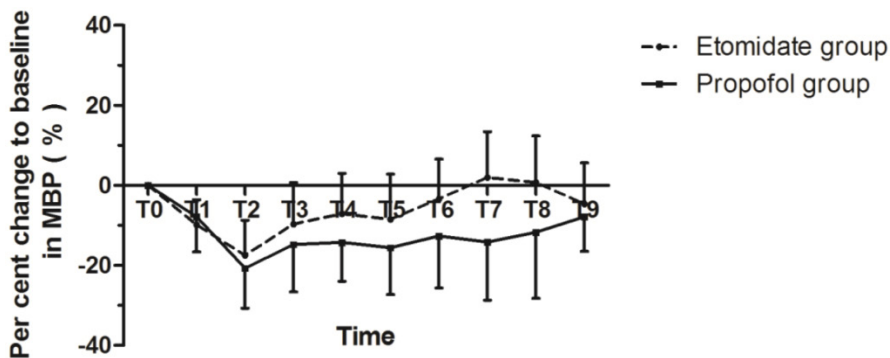
**Figure 1.** The time course of percent change to baseline in mean arterial pressure. $T_0$ = baseline values; $T_1$ = at 5 min after the patients received midazolam; $T_2$= when BIS was 50 after induction; $T_3$ = at scope intubation; $T_{4-10}$ = by 5-min intervals during the ERCP.
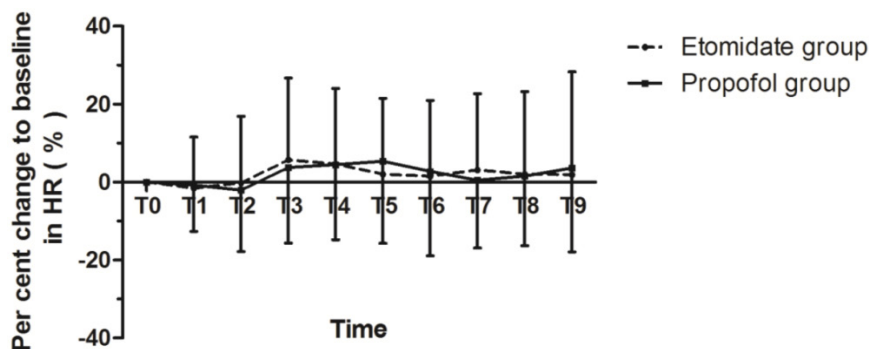
**Figure 2.** The time course of percent change to baseline in heart rate. $T_0$ = baseline values; $T_1$ = at 5 min after the patients received midazolam; $T_2$= when BIS was 50 after induction; $T_3$ = at scope intubation; $T_{4-10}$ = by 5-min intervals during the ERCP.
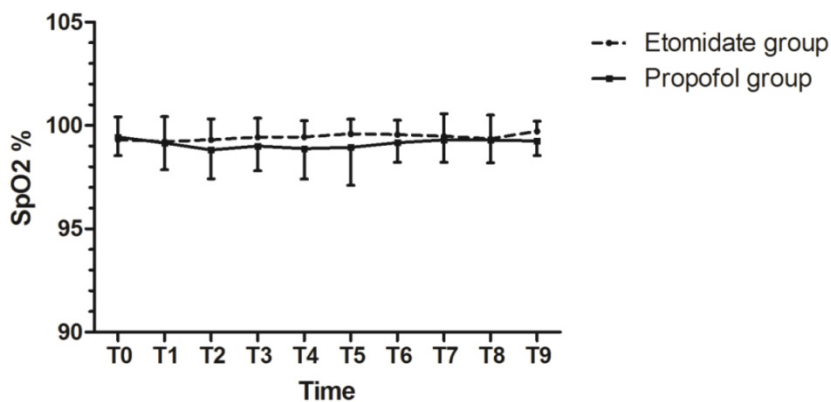
**Figure 3.** The $SpO_2$% levels over the designated time points. $T_0$ = baseline values; $T_1$ = at 5 min after the patients received midazolam; $T_2$= when BIS was 50 after induction; $T_3$ = at scope intubation; $T_{4-10}$ = by 5-min intervals during the ERCP.
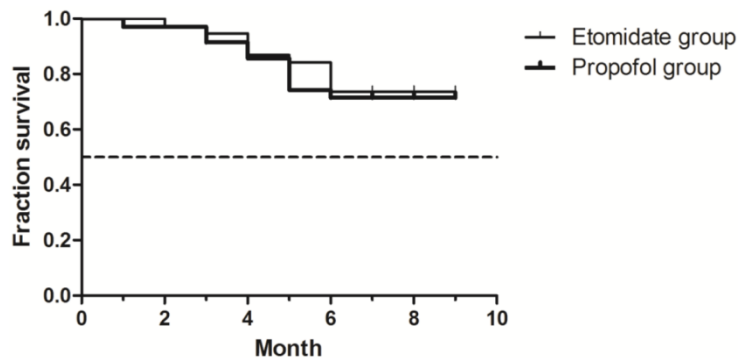
**Figure 4.** Survival analysis. Overall survival was defined as the interval between treatment and death of any cause.

# Discussion

In the present study, we investigated the influence of etomidate and propofol on haemodynamics in patients who underwent ERCP. The results showed that etomidate anesthesia during ERCP caused more stable haemodynamic responses compared with propofol.

In our endoscopy center, as a rule, the patients underwent ERCP in the prone position without tracheal intubation. It is known that the prone position may lead to inhibition of breathing because of airway obstruction. To reduce the incidence of respiratory depression caused by opioid agents, patients received pethidine pretreatment (100mg i.m.) instead of intravenous opioids. The absorption of intramuscular injection of drugs may be irregular and a confounding factor to the hemodynamic stability. Patients in both groups received pethidine pretreatment, therefore, the analgesia level could be comparable between two groups. In the present study, no patient experienced desaturation or apnoea, and the incidence of respiratory depression was much lower than in the other reports.[11] There are at least two factors that may help explain this. First, the low incidence of respiratory depression primarily due to the normal BMI in the studied Chinese patients. Secondly, patients with known severe respiratory disease (vital capacity and/or forced expiratory volume <50%) were excluded from this study. There were not enough data in obese patients and in patients with severe respiratory disease. Therefore, we must be careful of hypoxia during ERCP under the general anesthesia without tracheal intubation in these patients. New techniques, such as supraglottic jet oxygenation and ventilation, can be used to minimize hypoxia/hypercapnia during ERCP under infusion of etomidate or propofol in these patients.[16]

It has been known that sedation and anesthesia are routinely required during ERCP [17-19], because ERCP is a complex endoscopic procedure requiring a high level of patient cooperation. Various types of sedative and analgesic techniques have been used during ERCP procedure. It is generally accepted among gastroenterologists that propofol is a good hypnotic with rapid onset, rapid recovery, and minimal side effects.[17,18,20] It was reported that a target-controlled infusion system for administration of propofol provided safe and effective sedation during ERCP.[21] In a pilot study, it was shown that patient-maintained sedation with TCI propofol was safe and fully effective in 16 patients.[22] However, it was reported in a guideline of sedation and anesthesia in GI endoscopy that transient hypotension occurs in 4% to 7% of cases using propofol sedation and transient hypoxia occurs in 3% to 7% of cases.[23]

Etomidate is a nonbarbiturate hypnotic that induces anesthesia through GABA receptors in the central nervous system.[5] It has a rapid onset of action (≤1 minute) and a short duration of action (3-5 minutes). According to Miller's Anesthesia, "The properties of etomidate include haemodynamic stability, minimal respiratory depression, cerebral protection, and pharmacokinetics enabling rapid recovery after a single dose".[24] Etomidate's haemodynamic stability may be due to its unique lack of effect on the sympathetic nervous system and on baroreceptor function.[25]

Most patients who need ERCP suffer from obstructive jaundice. In the present study, the baseline of bilirubin was 118.2±117.8µmol/L in the etomidate group and 108.2±142.2 µmol/L in the propofol group. Patients with obstructive jaundice are more prone to develop hypotension and bradycardia during anesthesia induction and maintenance compared with non-jaundiced patients.[2,3] It was reported that patients with obstructive jaundice had decreased sensitivity in both the sympathetic and vagal components of the baroreflex.[4] Reich *et al.* suggested that "To avoid severe hypotension, alternatives to propofol anesthetic induction (e.g., etomidate) should be considered in patients older than 50 yr of age with ASA physical status ≥III."[26]

Myoclonus was a common side effect of etomidate for procedural sedation, which occurred in 20% to 45% of the patients in the Falk review.[8] Miner *et al.* noted a 20% incidence of myoclonus in their randomized clinical trial comparing etomidate with propofol.[10] In the present study, only one patient in the etomidate group experienced myoclonus, and required a brief period of mask ventilation and 50mg propofol (i.v.). The incidence of myoclonus in the present study was far lower than in other studies, which may be due to midazolam (2-2.5 mg i.v.) pretreatment in all patients before induction. Midazolam pretreatment reduces etomidate-induced myoclonic movements.[27,28] Furthermore, in the present study, etomidate was delivered at a rate of 30 µg•kg$^{-1}$•min$^{-1}$ by a Graseby 3500 syringe pump. This relatively "slow" delivering speed may also reduce the incidence of myoclonus.[29]

It was reported mean aortic and left ventricular end-diastolic pressure decreased 5 and 15 min after midazolam, 0.2 mg/kg iv. [30] Marty *et al.* noted that midazolam (0.3 mg/kg) used for induction of anesthesia resulted in a transient depression of baroreflex function and a sustained decrease of sympathetic tone. [31] However, Lim *et al.* found that co-induction with midazolam and propofol could prevent a marked BP decrease at tracheal intubation for induc-

tion in aged patients. [32] In the present study, the blood pressure on $T_1$ decreased compared with $T_0$, which may be partly attributable to small dose of midazolam (2-2.5 mg i.v.). However, because patients in both groups received the same dose of midazolam, the same effects would be expected in both groups.

Other side effects of etomidate are nausea and vomiting.[33] Vinson's study reported that 4% (5 of 134 patients) of patients experienced nausea and vomiting,[9] but in the present study, only one patient in each group experienced these side effects.

Our study had two limitations. The first is that we did not measure plasma cortisol and adrenocorti-cotropic hormone levels. It has been well known that adrenocortical suppression is one of the most important adverse effects of etomidate.[34] A recent paper compared much larger numbers of patients given etomidate and propofol (2616 patients were given etomidate, and 28,532 were given propofol), they found that etomidate was associated with an increased risk of 30-day mortality, cardiovascular morbidity, and prolonged hospital stay. They thought that etomidate should be used judiciously, considering that improved haemodynamic stability may be accompanied by substantially worse longer-term outcomes.[12] However, in a systematic review and meta-analysis of randomized controlled trials and observational studies, it was reported that single-dose etomidate does not increase mortality in patients with sepsis.[35] In the present study, no patient experienced adrenal crisis. There was no significant difference between groups for pancreatitis, cholangitis or sepsis after ERCP. Etomidate did not prolong hospital stay. Furthermore, there was no significant difference in the survival distributions between groups. Etomidate did not worsen longer-term outcomes. Differences in patient characteristics might contribute partly to the different results between our study and Ryu Komatsu's study: ASA I-III patients were enrolled in this study, while ASA III-IV patients were evaluated in Komatsu's study. Our data indicate that etomidate can safely be used in ASA I-III patients during ERCP.

The second limitation is that we did not measure respiratory rate, as the prone position makes it difficult to accurately count respiratory rate both artificially and automatically. In the present study, the effect on respiratory function was judged only by $SpO_2$, which may lead to missing subclinical respiratory depression.

In conclusion, our study demonstrated that etomidate anesthesia during ERCP caused more stable haemodynamic responses compared with propofol. Etomidate is an alternative to propofol during ERCP.

## Conflicts of Interest

The authors declare no conflicts of interest. The study complies with current ethical consideration.

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