**Name of Journal:** *World Journal of Clinical Cases*

**Manuscript NO:** 60689

**Manuscript Type:** ORIGINAL ARTICLE

***Clinical Trials Study***

**Etomidate *vs* propofol in coronary heart disease patients undergoing major noncardiac surgery: A randomized clinical trial**

Dai ZL *et al*. Etomidate *vs* propofol in CHD

Zhong-Liang Dai, Xing-Tao Cai, Wen-Li Gao, Miao Lin, Juan Lin, Yuan-Xu Jiang, Xin Jiang

**Zhong-Liang Dai, Xing-Tao Cai, Wen-Li Gao, Miao Lin, Juan Lin, Yuan-Xu Jiang,** Department of Anesthesiology, The First Affiliated Hospital of Southern University, The Second Clinical Medical College of Jinan University, Shenzhen People’s Hospital, Shenzhen 518020, Guangdong Province, China

**Xin Jiang,** Department of Geriatrics, The First Affiliated Hospital of Southern University, The Second Clinical Medical College of Jinan University, Shenzhen People’s Hospital, Shenzhen 518020, Guangdong Province, China

**Author contributions:** Dai ZL, Jiang YX, and Jiang X designed the study and analyzed the data; Cai XT, Gao WL and Lin M collected the data; Dai ZL, Lin J, and Cai XT interpreted the data; Dai ZL, Jiang YX, and Jiang X prepared the manuscript; all authors have read and approved the manuscript.

**Supported by** Shenzhen Municipal Science and Technology Foundation, No. JCYJ20170307100314152; Shenzhen Health Research Fund, No. SZLY2018011 and No. SZXJ2017029; Guangdong Medical Research Fund, No. A2018008 and No. A2019382; Scientific Research Fund of Shenzhen People’s Hospital, No. SYLY201706; and Shenzhen Key Medical Discipline Construction Fund, No. SZXK012.

**Corresponding author: Xin Jiang, MD, Doctor,** Department of Geriatrics, the First Affiliated Hospital of Southern University, the Second Clinical Medical College of Jinan University, Shenzhen People’s Hospital, No. 1017 Dongmen North Road, Luohu District, Shenzhen 518020, Guangdong Province, China. jiangxinsz@163.com

**Received:** November 10, 2020

**Revised:** December 17, 2020

**Accepted:** December 27, 2020

**Published online:** February 26, 2021

**Abstract**

BACKGROUND

The ideal depth of general anesthesia should achieve the required levels of hypnosis, analgesia, and muscle relaxation while minimizing physiologic responses to awareness. The choice of anesthetic strategy in patients with coronary heart disease (CHD) undergoing major noncardiac surgery is becoming an increasingly important issue as the population ages. This is because general anesthesia is associated with a risk of perioperative cardiac complications and death, and this risk is much higher in people with CHD.

AIM

To compare hemodynamic function and cardiovascular event rate between etomidate- and propofol-based anesthesia in patients with CHD.

METHODS

This prospective study enrolled consecutive patients (American Society of Anesthesiologists grade II/III) with stable CHD (New York Heart Association class I/II) undergoing major noncardiac surgery. The patients were randomly allocated to receive either etomidate/remifentanil-based or propofol/remifentanil-based general anesthesia. Randomization was performed using a computer-generated random number table and sequentially numbered, opaque, sealed envelopes. Concealment was maintained until the patient had arrived in the operating theater, at which point the consulting anesthetist opened the envelope. All patients, data collectors, and data analyzers were blinded to the type of anesthesia used. The primary endpoints were the occurrence of cardiovascular events (bradycardia, tachycardia, hypotension, ST-T segment changes, and ventricular premature beats) during anesthesia and cardiac troponin I level at 24 h. The secondary endpoints were hemodynamic parameters, bispectral index, and use of vasopressors during anesthesia.

RESULTS

The final analysis included 40 patients in each of the propofol and etomidate groups. The incidences of bradycardia, hypotension, ST-T segment changes, and ventricular premature beats during anesthesia were significantly higher in the propofol group than in the etomidate group (*P* < 0.05 for all). The incidence of tachycardia was similar between the two groups. Cardiac troponin I levels were comparable between the two groups both before the induction of anesthesia and at 24 h after surgery. When compared with the etomidate group, the propofol group had significantly lower heart rates at 3 min after the anesthetic was injected (T1) and immediately after tracheal intubation (T2), lower systolic blood pressure at T1, and lower diastolic blood pressure and mean arterial pressure at T1, T2, 3 min after tracheal intubation, and 5 min after tracheal intubation (*P* < 0.05 for all). Vasopressor use was significantly more in the propofol group than in the etomidate group during the induction and maintenance periods (*P* < 0.001).

CONCLUSION

In patients with CHD undergoing noncardiac major surgery, etomidate-based anesthesia is associated with fewer cardiovascular events and smaller hemodynamic changes than propofol-based anesthesia.

**Key Words:** Etomidate; Propofol; General anesthesia; Coronary heart disease; Hemodynamic; Cardiovascular events

**©The** **Author(s) 2021.** Published by Baishideng Publishing Group Inc. All rights reserved.

**Citation:** Dai ZL, Cai XT, Gao WL, Lin M, Lin J, Jiang YX, Jiang X. Etomidate *vs* propofol in coronary heart disease patients undergoing major noncardiac surgery: A randomized clinical trial. *World J Clin Cases* 2021; 9(6): 1293-1303

**URL:** https://www.wjgnet.com/2307-8960/full/v9/i6/1293.htm

**DOI:** https://dx.doi.org/10.12998/wjcc.v9.i6.1293

**Core Tip:** The results show that in patients with coronary heart disease undergoing noncardiac major surgery, etomidate-based anesthesia was associated with fewer cardiovascular events and smaller hemodynamic changes than propofol-based anesthesia.

**INTRODUCTION**

The ideal depth of general anesthesia should achieve the required levels of hypnosis, analgesia and muscle relaxation while minimizing physiologic responses to awareness such as tachycardia, hypertension, sweating, lacrimation, increased skeletal muscle tone, and spontaneous movement[[1](#_ENREF_1),[2](#_ENREF_2)]. The choice of anesthetic strategy in patients with coronary heart disease (CHD) undergoing major noncardiac surgery is becoming an increasingly important issue as the population ages. This is because general anesthesia is associated with a risk of perioperative cardiac complications and death, and this risk is much higher in people with CHD. Perioperative cardiac complications including myocardial infarction (MI) have been reported in around 15% of patients with CHD who undergo noncardiac surgery[[3](#_ENREF_3),[4](#_ENREF_4)], although even higher rates have been described in some studies[[5](#_ENREF_5)]. Furthermore, preoperative CHD is associated with an approximately 6-fold increased odds of reintubation following surgery under general anesthesia[[6](#_ENREF_6)]. It is thus essential to utilize strategies that maintain hemodynamic stability, adequate oxygenation and a good analgesic effect while minimizing the risk of perioperative ischemia, and this requires a multidisciplinary approach[[7-9](#_ENREF_7)]. Recommendations have been made regarding the perioperative medical management of CHD in patients undergoing noncardiac surgery[[10](#_ENREF_10)]. The type of anesthesia used may also affect perioperative cardiac outcomes in patients[[11](#_ENREF_11)].

Propofol is an intravenous anesthetic agent that is widely used for the induction and maintenance of general anesthesia. However, propofol has various effects on the cardiovascular system including a decrease in blood pressure[[12-14](#_ENREF_12)], impaired cardiac contraction[[15](#_ENREF_15)], and (rarely) the induction of arrhythmia[[16](#_ENREF_16)]. Propofol has also been reported to compromise cardiovascular function in patients with CHD[[17](#_ENREF_17)]. A study of 12 patients with CHD found that propofol anesthesia was associated with an increase in heart rate, reductions in arterial blood pressure, myocardial blood flow, and myocardial oxygen consumption, and in one patient an elevation in myocardial lactate production[[18](#_ENREF_18)]. This latter finding and the observation of ischemic electrocardiogram (ECG) changes during propofol anesthesia[[19](#_ENREF_19)] suggest that propofol can induce myocardial ischemia in at-risk patients.

Etomidate is an alternative intravenous anesthetic agent that has a rapid onset and a short duration of action. There is published evidence that etomidate may have smaller effects on the cardiovascular system than propofol. For example, when compared with propofol, etomidate has been reported to cause smaller reductions in blood pressure, heart rate, arterial elastance, and systemic vascular resistance during the induction of anesthesia[[19](#_ENREF_19),[20](#_ENREF_20)]. However, some studies have concluded that propofol may have advantages over etomidate with regard to minimizing the stress response and alleviating ischemic ECG changes[[19](#_ENREF_19),[21](#_ENREF_21)]. Thus, further research is needed to establish which of these agents is preferable in patients with CHD.

The aim of the present study was to compare hemodynamic function and cardiovascular event rate between etomidate- and propofol-based anesthesia in patients with CHD undergoing major noncardiac surgery.

**MATERIALS AND METHODS**

***Study design and patients***

This prospective, randomized clinical trial enrolled consecutive patients with stable CHD undergoing major noncardiac surgery at the Department of Anesthesiology, Shenzhen People’s Hospital, Guangdong Province, China between July 2014 and December 2015. The inclusion criteria were: (1) Age 52-88 years; (2) American Society of Anesthesiologists grade II or III; (3) A clinical history of stable angina pectoris or myocardial infarction; (4) Angiographically-confirmed stenosis of > 50% in at least one coronary artery; (5) Cardiac function graded as New York Heart Association class I or II; (6) Scheduled for major gastrointestinal, hepatobiliary, or thyroid surgery; and (7) Expected duration of hospitalization ≥ 24 h. The exclusion criteria were: (1) Scheduled for emergency surgery or cardiac surgery; (2) Congenital heart disease, rheumatic heart disease, cardiomyopathy, valvular disease, or significant left ventricular hypertrophy; (3) Myocardial infarction, percutaneous coronary intervention, or other serious cardiopulmonary dysfunction in the previous 3 mo; (4) Dysfunction of the liver, kidney, or adrenal cortex; (5) History of abnormal bleeding; (6) Adverse reactions to propofol or etomidate; (7) Implanted cardiac pacemaker; (8) Hypertension of grade 3 or above; (9) Hypotension or shock; (10) Body mass index > 30 kg/m2; and (11) Participation in another study that might interfere with the endpoints of the current trial.

The study was approved by the Ethics Committee of Shenzhen People’s Hospital (LL-KT-2014211) and conducted according to the Declaration of Helsinki. All patients provided written informed consent after having been provided with detailed information about the study aims, procedures, and risks. ChiCTR1900025174. The trial was registered in Chinese Clinical Trial Registry on August 15, 2019 (ChiCTR1900025174) and is available at http://www.chictr.org.cn/showproj.aspx?proj=42063.

***Randomization and grouping***

The patients were randomly allocated to receive either etomidate/remifentanil-based or propofol/remifentanil-based general anesthesia. Randomization was performed using a computer-generated random number table and sequentially numbered, opaque, sealed envelopes. Concealment was maintained until the patient had arrived in the operating theater, at which point the consulting anesthetist opened the envelope. All patients, data collectors, and data analyzers were blinded to the type of anesthesia used.

***Calculation of sample size***

For this superiority trial, a 10% difference in the rate of myocardial ischemia between groups was regarded as clinically relevant based on previous studies[[9](#_ENREF_9),[13](#_ENREF_13),[14](#_ENREF_14)]. Assuming an alpha of 5% and a test power of 0.8, power analysis indicated that a difference of 10% would be detected with a total sample size of 160 (or 80 per group). Assuming a loss to follow-up of 20%, each group would need to include 100 patients at enrolment.

***Anesthesia and monitoring***

The same main anesthetist (Dr Li) was present at all the operations, and all procedures were performed by the same surgical team. The patients were admitted the day before surgery and fasted for at least 8 h before the operation. Some patients continued to receive an antihypertensive agent (captopril) until the morning of surgery. On arrival in the operating theater, an intravenous catheter was inserted into a large forearm vein, and standard monitoring was initiated including non-invasive arterial blood pressure (Datex-Ohmeda, Helsinki, Finland) and bispectral index (BIS; Aspect Medical Systems, Newton, MA, United States) monitoring. Vital parameters such as heart rate (HR), systolic blood pressure (SBP), diastolic blood pressure (DBP), and mean arterial pressure (MAP) were assessed at regular intervals.

Patients in both groups received oral midazolam (0.04 mg/kg; Enhua Pharmaceutical Co. Ltd., Xuzhou, China) at least 1 h before induction of anesthesia. An infusion of remifentanil (4 μg/kg; Renfu Pharmaceutical Group Co. Ltd., Yichang, China) was started during pre-oxygenation *via* a face mask, and anesthesia was induced 3 min later by the administration of cisatracurium (0.2 mg/kg; Jiangsu Hengrui Pharmaceutical Co. Ltd., Lianyungang, China) with either etomidate (0.3 mg/kg; Enhua Pharmaceutical Co. Ltd.; etomidate group) or propofol (2.0 mg/kg; Fresenius Kabi, Uppsala, Sweden; propofol group). The trachea was intubated, and mechanical ventilation was started with a tidal volume of 8 mL/kg, a ventilatory frequency that maintained end-tidal Pco2 between 35 and 45 mmHg, and a fraction of inspired oxygen (FIO2) of 1.0 (PhysioFlex closed-circuit anesthesia machine, Dräger, Lübeck, Germany).

Baseline hemodynamic data were recorded after at least 5 min without further changes in HR or arterial pressure. The BIS was maintained at a value of 45-60 to achieve a suitable depth of anesthesia with very low awareness possibility. The remifentanil infusion was continued and increased in increments of 0.05 mg/kg/min if one of the following occurred: Sudden increase in HR or arterial pressure by > 20%, sweating, or spontaneous movements.

For maintenance of anesthesia in the propofol group, 1% propofol (1.5-3.0 μg/mL) was administered by target-controlled infusion (Alaris Pk syringe pump, Cardinal Health, Rolle, Switzerland) according to a modified Marsh pharmacokinetic model (ke0 of 1.21 min-1; plasma mode using real weight) starting at an initial target concentration of 1.0 μg/mL and increasing at a rate of 0.5 μg/mL each minute until a plasma concentration (Cp) of 2.5 μg/mL was attained. In the etomidate group, anesthesia was maintained by the continuous infusion of etomidate emulsion at a constant rate (10-20 μg/kg/min). Intermittent bolus injections of cisatracurium were used to maintain full muscle relaxation. No other anesthetic agents were administered until 30 min before the operation finished.

Thirty minutes before the end of surgery, 0.1 mg fentanyl and 50 mg flurbiprofen were administrated intravenously, and the cisatracurium infusion was stopped. Five minutes before the end of the operation, 3 mg granisetron was administrated by intravenous injection. The infusion of remifentanil and etomidate/propofol was stopped at the end of surgery. Neostigmine was used to reverse residual muscle relaxation after spontaneous respiration had recovered. Awakening was considered as the moment when the patient opened their eyes after being called by their name. Extubation was performed when the following conditions were met: Recovery of the cough and swallowing reflexes; recovery of consciousness and awakening; tidal volume > 6 mL/kg; respiratory rate 12-30 times/min; head elevation for > 2 s; and normal BP, HR, and ECG findings.

***Measurement of clinical variables***

SBP, DBP, HR, ST-T interval, and BIS were recorded immediately before the induction of anesthesia (T0), 3 min after the anesthetic was injected (T1), immediately after tracheal intubation (T2), 3 min after tracheal intubation (T3), and 5 min after tracheal intubation (T4). The levels of cardiac troponin I (cTnI) were measured before the induction of anesthesia and 24 h after surgery to determine the extent of any myocardial injury.

The patients were followed for 24 h. The primary endpoints were the occurrence of cardiovascular events (bradycardia, tachycardia, hypotension, ST-T segment changes, and ventricular premature beats) during anesthesia and cTnI level at 24 h. The secondary endpoints were hemodynamic parameters (SBP, DBP, MAP, and HR), BIS and use of vasopressors during anesthesia.

***Statistical analysis***

SPSS 15.0 (SPSS Inc., Chicago, IL, United States) was used for data analyses, and Microsoft Excel and Word (Microsoft Corp., Redmond, WA, United States) were used to generate graphs and tables. Measurement data were tested for normality using the Kolmogorov-Smirnov test. Quantitative data are expressed as the mean ± standard deviation and were compared between groups using Student’s t-test with Bonferroni correction. Categorical data are presented as *n* (%) and were compared between groups using the chi-squared test or Fisher’s exact test. *P* < 0.05 was taken to indicate statistical significance.

**RESULTS**

***Baseline clinical characteristics of the study participants***

Among 100 patients screened for eligibility, 15 were excluded because they did not meet the inclusion criteria, and 5 were excluded because they refused to participate (Figure 1). Therefore, a total of 80 patients were included in the final analysis, with 40 patients in each group. There were no significant differences between groups in sex, age, height, weight, or type of surgery (Table 1).

***Primary endpoints***

The incidences of bradycardia, hypotension, ST-T segment changes, and ventricular premature beats during anesthesia were significantly higher in the propofol group than in the etomidate group (*P* < 0.05 for all; Table 2). The incidence of tachycardia did not differ significantly between groups (Table 2). cTnI levels in the propofol and etomidate groups were comparable both before the induction of anesthesia (0.009 ± 0.003 ng/mL and 0.010 ± 0.001 ng/mL, respectively) and 24 h after surgery (0.012 ± 0.005 ng/mL and 0.011 ± 0.002 ng/mL, respectively).

***Secondary endpoints***

There were no significant differences between the propofol and etomidate groups in HR, SBP, DBP, or MAP immediately before the induction of anesthesia (Table 3). Both groups exhibited reductions in HR, SBP, DBP, and MAP following the induction of anesthesia, but these changes were more prominent in the propofol group (Table 3). When compared with the etomidate group, the propofol group had significantly lower HR at 3 min after anesthetic injection and immediately after tracheal intubation, lower SBP at 3 min after anesthetic injection, and lower DBP and MAP at all four time points after the induction of anesthesia (*P* < 0.05 for all; Table 3).

None of the observed changes in HR required intervention. All cases of hypotension (a decrease in MAP to ≤ 70% of the baseline value) were successfully treated with single injections of phenylephrine or ephedrine. Notably, vasopressor use was significantly higher in the propofol group than in the etomidate group during the induction and maintenance periods (*P* < 0.001 for both ephedrine and phenylephrine use; Table 4).

The BIS values were not significantly different between the propofol and etomidate groups at all time points (Table 5).

**DISCUSSION**

An important finding of the present study was that the incidences of bradycardia, hypotension, ST-T segment changes, and ventricular premature beats in patients with CHD undergoing noncardiac major surgery were significantly higher for propofol-based general anesthesia than for etomidate-based anesthesia. Furthermore, in comparison with the etomidate group, the propofol group had significantly lower HR, SBP, DBP, and MAP at various time points after the induction of anesthesia. Additionally, vasopressor use was significantly more in the propofol group than in the etomidate group during the induction and maintenance periods. The above data suggest that etomidate-based anesthesia may be preferable to propofol-based anesthesia in patients with CHD undergoing noncardiac major surgery.

Monitored anesthesia care is frequently considered a means to increase safety when anesthetists are confronted with a patient who has complex cardiac physiology. This is understandable because general anesthesia is known to be associated with a risk of perioperative cardiac complications, and this risk is particularly high in patients with CHD[[3-5](#_ENREF_3)]. In part, the risks of general anesthesia in patients with CHD may be related to their hemodynamic effects. In the present study, the reductions in HR, SBP, DBP, and MAP during the induction of anesthesia were significantly greater for propofol (supplemented by remifentanil) than for etomidate (supplemented by remifentanil). Our findings are in good agreement with previous research indicating that propofol decreases blood pressure[[12-14](#_ENREF_12)] and impairs cardiovascular function in patients with CHD[[17](#_ENREF_17),[18](#_ENREF_18)] whereas etomidate is associated with smaller inhibitory effects on hemodynamics in patients with CHD[[19](#_ENREF_19),[20](#_ENREF_20)]. Notably, etomidate has also been reported to cause less hemodynamic instability than propofol in the setting of congenital heart disease and impaired cardiac function[[22](#_ENREF_22)].

Adult patients with CHD are now surviving longer than ever before, and it is becoming increasingly apparent that even the simplest coronary lesions can be associated with long-term complications. A previous study concluded that propofol anesthesia was associated with decreases in arterial blood pressure, myocardial blood flow, and myocardial oxygen consumption and (in one case) an increase in myocardial lactate production[[18](#_ENREF_18)], while another described ischemic ECG changes during propofol anesthesia[[19](#_ENREF_19)]. These previous findings suggest that propofol-based general anesthesia might induce myocardial ischemia in certain patients with CHD. In the present analysis, propofol-based anesthesia was associated with significantly higher incidences of bradycardia, hypotension, ST-T segment abnormalities, and ventricular premature beats than etomidate-based anesthesia, implying that etomidate may be associated with a lower risk of these cardiovascular events than propofol, perhaps because etomidate is associated with better hemodynamic stability than propofol[[23](#_ENREF_23),[24](#_ENREF_24)]. Although there is some evidence that propofol may have advantages over etomidate with regard to reducing the stress response and minimizing ischemic ECG changes[[19](#_ENREF_19),[21](#_ENREF_21)], our results suggest that ST-T segment abnormalities and other cardiovascular events occur less frequently for etomidate than for propofol during the induction of anesthesia.

Etomidate, an imidazole-derived ultrashort-acting nonbarbiturate hypnotic, is frequently used to induce anesthesia in critically ill patients because of its hemodynamic safety, rapid onset, and short duration of action[[25](#_ENREF_25)]. However, although etomidate offers the advantage of minimizing hypotension that can cause coronary hypoperfusion, dysrhythmia, and cardiac arrest, a previous clinical study reported that induction of anesthesia with etomidate rather than propofol was associated with increased 30 d mortality and cardiovascular morbidity after noncardiac surgery as well as a prolonged duration of hospitalization[[26](#_ENREF_26)]. It is possible that some of the effects reported in this earlier study resulted from a suppression of adrenocortical function by etomidate[[27](#_ENREF_27)]. However, this prior study was retrospective and the patients were not randomized to etomidate- or propofol-based anesthesia, so the results may have been influenced by confounding factors. Indeed, other investigations did not find a longer duration of hospital stay or increased mortality for etomidate-based anesthesia than for propofol-based anesthesia[[28](#_ENREF_28),[29](#_ENREF_29)].

The present study did not detect any notable increase in cTnI level at 24 h after surgery in either the propofol or etomidate group. Nevertheless, we would recommend postoperative troponin monitoring in all patients with known cardiovascular risk who are undergoing major surgery, as suggested by others[[30-33](#_ENREF_30)]. Without early postoperative monitoring of troponin, physicians would be likely to miss 2/3 of the MIs that occur, and asymptomatic MIs carry the same high risk of 30 d mortality as symptomatic MIs[[32](#_ENREF_32)].

Our study has several limitations. First, the sample size was small, so the study may have been underpowered to detect some real differences between groups. Second, this was a single-center study, so the generalizability of the findings is not known. Third, the follow-up period was only 24 h, so longer-term outcomes such as duration of hospital stay, cardiovascular morbidity, and 30 d mortality were not evaluated. Fourth, as with any observational study, unknown confounding factors may have influenced the results.

**CONCLUSION**

For patients with CHD undergoing noncardiac major surgery, etomidate-based anesthesia may be preferable to propofol-based anesthesia due to a lower incidence of cardiovascular events and smaller hemodynamic changes.

**ARTICLE HIGHLIGHTS**

***Research background***

The choice of anesthetic strategy in patients with coronary heart disease (CHD) undergoing major noncardiac surgery is becoming an increasingly important issue as the population ages.

***Research motivation***

Perioperative cardiac complications including myocardial infarction have been reported in around 15% of patients with CHD who undergo noncardiac surgery. It is thus essential to utilize strategies that maintain hemodynamic stability, adequate oxygenation, and a good analgesic effect while minimizing the risk of perioperative ischemia, and this requires a multidisciplinary approach.

***Research objectives***

To compare hemodynamic function and cardiovascular event rate between etomidate- and propofol-based anesthesia in patients with CHD.

***Research methods***

This prospective, randomized clinical trial enrolled consecutive patients with stable CHD undergoing major noncardiac surgery. The patients were randomly allocated to receive either etomidate/remifentanil-based or propofol/remifentanil-based general anesthesia.

***Research results***

The final analysis included 40 patients in each group. The incidences of bradycardia, hypotension, ST-T segment changes, and ventricular premature beats during anesthesia were significantly higher in the propofol group than in the etomidate group (*P* < 0.05 for all).

***Research conclusions***

In patients with CHD undergoing noncardiac major surgery, etomidate-based anesthesia was associated with fewer cardiovascular events and smaller hemodynamic changes than propofol-based anesthesia.

***Research perspectives***

In the future, a large prospective randomized study will definitively address the effect of etomidate on postoperative outcomes in patients with coronary heart disease undergoing major noncardiac surgery.

**ACKNOWLEDGEMENTS**

We thank Hai-Bo Wang PhD from Peking University for statistical data preparation. We also thank Professor Zheng-Yuan Xia from Hong Kong University for assistance in manuscript preparation. We are grateful to Zhong-Jun Zhang, Xue-Ping Zhang, and Ya-Li Li for their crucial role in patient recruitment and data collection.

**REFERENCES**

1 **Brown EN**, Pavone KJ, Naranjo M. Multimodal General Anesthesia: Theory and Practice. *Anesth Analg* 2018; **127**: 1246-1258 [PMID: 30252709 DOI: 10.1213/ANE.0000000000003668]

2 **Rani DD**, Harsoor S. Depth of general anaesthesia monitors. *Indian J Anaesth* 2012; **56**: 437-441 [PMID: 23293381 DOI: 10.4103/0019-5049.103956]

3 **Seki M**, Kashimoto S, Nagata O, Yoshioka H, Ishiguro T, Nishimura K, Honda O, Sakamoto A, Omi A, Ogihara Y, Fujimoto K, Iwade M, Yamada T, Nomura M, Takeda J. Are the incidences of cardiac events during noncardiac surgery in Japan the same as in the United States and Europe? *Anesth Analg* 2005; **100**: 1236-1240, table of contents [PMID: 15845660 DOI: 10.1213/01.ANE.0000152009.49024.F1]

4 **Yamada T**, Nomura M, Iwade M, Omi A, Kashimoto S, Yoshioka H, Kikuchi T, Fujimoto K, Honda O, Seki M, Ishiguro T, Takeda J. [Multicenter study of cardiac events and anesthetic management of patients with ischemic heart diseases undergoing noncardiac surgery]. *Masui* 2000; **49**: 673-679 [PMID: 10885253]

5 **Varma MK**, Puri GD, Chari P, Verma JS, Kohli KK. Perioperative myocardial infarction in coronary artery disease patients and 'at-risk' for coronary artery disease patients undergoing non-cardiac surgery. *Natl Med J India* 1996; **9**: 214-217 [PMID: 8937059]

6 **Wang K**, Yin Y. Risk Factors and Prognosis of Reintubation Following Surgeries under General Anesthesia. *Zhongguo Yi Xue Ke Xue Yuan Xue Bao* 2017; **39**: 145-149 [PMID: 28270298 DOI: 10.3881/j.issn.1000-503X.2017.01.024]

7 **Fellahi JL**, Godier A, Benchetrit D, Berthier F, Besch G, Bochaton T, Bonnefoy-Cudraz E, Coriat P, Gayat E, Hong A, Jenck S, Le Gall A, Longrois D, Martin AC, Pili-Floury S, Piriou V, Provenchère S, Rozec B, Samain E, Schweizer R, Billard V. Perioperative management of patients with coronary artery disease undergoing non-cardiac surgery: Summary from the French Society of Anaesthesia and Intensive Care Medicine 2017 convention. *Anaesth Crit Care Pain Med* 2018; **37**: 367-374 [PMID: 29567130 DOI: 10.1016/j.accpm.2018.02.021]

8 **Sellevold OF**, Stenseth R. [Non-cardiac surgery in patients with cardiac disease]. *Tidsskr Nor Laegeforen* 2010; **130**: 623-627 [PMID: 20349010 DOI: 10.4045/tidsskr.08.0309]

9 **Sear JW**, Higham H. Issues in the perioperative management of the elderly patient with cardiovascular disease. *Drugs Aging* 2002; **19**: 429-451 [PMID: 12149050 DOI: 10.2165/00002512-200219060-00003]

10 **Feringa HH**, Bax JJ, Poldermans D. Perioperative medical management of ischemic heart disease in patients undergoing noncardiac surgery. *Curr Opin Anaesthesiol* 2007; **20**: 254-260 [PMID: 17479031 DOI: 10.1097/ACO.0b013e3280c60c50]

11 **Gal J**, Bogar L, Acsady G, Kertai MD. Cardiac risk reduction in non-cardiac surgery: the role of anaesthesia and monitoring techniques. *Eur J Anaesthesiol* 2006; **23**: 641-648 [PMID: 16723061 DOI: 10.1017/S0265021506000640]

12 **Farhan M**, Hoda MQ, Ullah H. Prevention of hypotension associated with the induction dose of propofol: A randomized controlled trial comparing equipotent doses of phenylephrine and ephedrine. *J Anaesthesiol Clin Pharmacol* 2015; **31**: 526-530 [PMID: 26702213 DOI: 10.4103/0970-9185.169083]

13 **Pensado A**, Molins N, Alvarez J. [Cardiovascular effects of a single dose of propofol in coronary patients with good ventricular function]. *Rev Esp Anestesiol Reanim* 1994; **41**: 147-151 [PMID: 7914708]

14 **Galletly DC**, Short TG. Total intravenous anaesthesia using propofol infusion--50 consecutive cases. *Anaesth Intensive Care* 1988; **16**: 150-157 [PMID: 2899404 DOI: 10.1177/0310057X8801600204]

15 **Yang HS**, Song BG, Kim JY, Kim SN, Kim TY. Impact of propofol anesthesia induction on cardiac function in low-risk patients as measured by intraoperative Doppler tissue imaging. *J Am Soc Echocardiogr* 2013; **26**: 727-735 [PMID: 23622885 DOI: 10.1016/j.echo.2013.03.016]

16 **Wutzler A**, De Asmundis C, Matsuda H, Bannehr M, Loehr L, Voelk K, Jungmann J, Huemer M, Attanasio P, Parwani A, Boldt LH, Brugada P, Haverkamp W. Effects of propofol on ventricular repolarization and incidence of malignant arrhythmias in adults. *J Electrocardiol* 2018; **51**: 170-174 [PMID: 29174097 DOI: 10.1016/j.jelectrocard.2017.11.003]

17 **Baumert JH**, Hein M, Hecker KE, Satlow S, Neef P, Rossaint R. Xenon or propofol anaesthesia for patients at cardiovascular risk in non-cardiac surgery. *Br J Anaesth* 2008; **100**: 605-611 [PMID: 18344556 DOI: 10.1093/bja/aen050]

18 **Stephan H**, Sonntag H, Schenk HD, Kettler D, Khambatta HJ. Effects of propofol on cardiovascular dynamics, myocardial blood flow and myocardial metabolism in patients with coronary artery disease. *Br J Anaesth* 1986; **58**: 969-975 [PMID: 3489478 DOI: 10.1093/bja/58.9.969]

19 **Lischke V**, Probst S, Behne M, Kessler P. [ST segment changes in the ECG. Anesthesia induction with propofol, etomidate or midazolam in patients with coronary heart disease]. *Anaesthesist* 1993; **42**: 435-440 [PMID: 8363027]

20 **Haessler R**, Madler C, Klasing S, Schwender D, Peter K. Propofol/fentanyl versus etomidate/fentanyl for the induction of anesthesia in patients with aortic insufficiency and coronary artery disease. *J Cardiothorac Vasc Anesth* 1992; **6**: 173-180 [PMID: 1568003 DOI: 10.1016/1053-0770(92)90193-b]

21 **Singh R**, Choudhury M, Kapoor PM, Kiran U. A randomized trial of anesthetic induction agents in patients with coronary artery disease and left ventricular dysfunction. *Ann Card Anaesth* 2010; **13**: 217-223 [PMID: 20826962 DOI: 10.4103/0971-9784.69057]

22 **Andropoulos DB**, Stayer SA, Skjonsby BS, East DL, McKenzie ED, Fraser CD. Anesthetic and perioperative outcome of teenagers and adults with congenital heart disease. *J Cardiothorac Vasc Anesth* 2002; **16**: 731-736 [PMID: 12486655 DOI: 10.1053/jcan.2002.128410]

23 **Aggarwal S**, Goyal VK, Chaturvedi SK, Mathur V, Baj B, Kumar A. A comparative study between propofol and etomidate in patients under general anesthesia. *Braz J Anesthesiol* 2016; **66**: 237-241 [PMID: 27108818 DOI: 10.1016/j.bjane.2014.10.005]

24 **Kaushal RP**, Vatal A, Pathak R. Effect of etomidate and propofol induction on hemodynamic and endocrine response in patients undergoing coronary artery bypass grafting/mitral valve and aortic valve replacement surgery on cardiopulmonary bypass. *Ann Card Anaesth* 2015; **18**: 172-178 [PMID: 25849685 DOI: 10.4103/0971-9784.154470]

25 **Cherfan AJ**, Arabi YM, Al-Dorzi HM, Kenny LP. Advantages and disadvantages of etomidate use for intubation of patients with sepsis. *Pharmacotherapy* 2012; **32**: 475-482 [PMID: 22488264 DOI: 10.1002/j.1875-9114.2012.01027.x]

26 **Komatsu R**, You J, Mascha EJ, Sessler DI, Kasuya Y, Turan A. Anesthetic induction with etomidate, rather than propofol, is associated with increased 30-day mortality and cardiovascular morbidity after noncardiac surgery. *Anesth Analg* 2013; **117**: 1329-1337 [PMID: 24257383 DOI: 10.1213/ANE.0b013e318299a516]

27 **Albert SG**, Ariyan S, Rather A. The effect of etomidate on adrenal function in critical illness: a systematic review. *Intensive Care Med* 2011; **37**: 901-910 [PMID: 21373823 DOI: 10.1007/s00134-011-2160-1]

28 **Basciani RM**, Rindlisbacher A, Begert E, Brander L, Jakob SM, Etter R, Carrel T, Eberle B. Anaesthetic induction with etomidate in cardiac surgery: A randomised controlled trial. *Eur J Anaesthesiol* 2016; **33**: 417-424 [PMID: 26914224 DOI: 10.1097/EJA.0000000000000434]

29 **Romito B**, Stone J, Ning N, Yin C, Llano EM, Liu J, Somanath K, Lee CT, Matchett G. How Drug Shortages Affect Clinical Care: The Case of the Surgical Anesthetic Propofol. *Hosp Pharm* 2015; **50**: 798-805 [PMID: 26912921 DOI: 10.1310/hpj5009-798]

30 **Biccard BM**, Devereaux PJ, Rodseth RN. Cardiac biomarkers in the prediction of risk in the non-cardiac surgery setting. *Anaesthesia* 2014; **69**: 484-493 [PMID: 24738805 DOI: 10.1111/anae.12635]

31 **Vascular Events In Noncardiac Surgery Patients Cohort Evaluation (VISION) Study Investigators.**, Devereaux PJ, Chan MT, Alonso-Coello P, Walsh M, Berwanger O, Villar JC, Wang CY, Garutti RI, Jacka MJ, Sigamani A, Srinathan S, Biccard BM, Chow CK, Abraham V, Tiboni M, Pettit S, Szczeklik W, Lurati Buse G, Botto F, Guyatt G, Heels-Ansdell D, Sessler DI, Thorlund K, Garg AX, Mrkobrada M, Thomas S, Rodseth RN, Pearse RM, Thabane L, McQueen MJ, VanHelder T, Bhandari M, Bosch J, Kurz A, Polanczyk C, Malaga G, Nagele P, Le Manach Y, Leuwer M, Yusuf S. Association between postoperative troponin levels and 30-day mortality among patients undergoing noncardiac surgery. *JAMA* 2012; **307**: 2295-2304 [PMID: 22706835 DOI: 10.1001/jama.2012.5502]

32 **Devereaux PJ**, Xavier D, Pogue J, Guyatt G, Sigamani A, Garutti I, Leslie K, Rao-Melacini P, Chrolavicius S, Yang H, Macdonald C, Avezum A, Lanthier L, Hu W, Yusuf S; POISE (PeriOperative ISchemic Evaluation) Investigators. Characteristics and short-term prognosis of perioperative myocardial infarction in patients undergoing noncardiac surgery: a cohort study. *Ann Intern Med* 2011; **154**: 523-528 [PMID: 21502650 DOI: 10.7326/0003-4819-154-8-201104190-00003]

33 **Thygesen K**, Alpert JS, Jaffe AS, Simoons ML, Chaitman BR, White HD; Joint ESC/ACCF/AHA/WHF Task Force for Universal Definition of Myocardial Infarction; Authors/Task Force Members Chairpersons, Thygesen K, Alpert JS, White HD; Biomarker Subcommittee, Jaffe AS, Katus HA, Apple FS, Lindahl B, Morrow DA; ECG Subcommittee, Chaitman BR, Clemmensen PM, Johanson P, Hod H; Imaging Subcommittee, Underwood R, Bax JJ, Bonow JJ, Pinto F, Gibbons RJ; Classification Subcommittee, Fox KA, Atar D, Newby LK, Galvani M, Hamm CW; Intervention Subcommittee, Uretsky BF, Steg PG, Wijns W, Bassand JP, Menasche P, Ravkilde J; Trials & Registries Subcommittee, Ohman EM, Antman EM, Wallentin LC, Armstrong PW, Simoons ML; Trials & Registries Subcommittee, Januzzi JL, Nieminen MS, Gheorghiade M, Filippatos G; Trials & Registries Subcommittee, Luepker RV, Fortmann SP, Rosamond WD, Levy D, Wood D; Trials & Registries Subcommittee, Smith SC, Hu D, Lopez-Sendon JL, Robertson RM, Weaver D, Tendera M, Bove AA, Parkhomenko AN, Vasilieva EJ, Mendis S; ESC Committee for Practice Guidelines (CPG), Bax JJ, Baumgartner H, Ceconi C, Dean V, Deaton C, Fagard R, Funck-Brentano C, Hasdai D, Hoes A, Kirchhof P, Knuuti J, Kolh P, McDonagh T, Moulin C, Popescu BA, Reiner Z, Sechtem U, Sirnes PA, Tendera M, Torbicki A, Vahanian A, Windecker S; Document Reviewers, Morais J, Aguiar C, Almahmeed W, Arnar DO, Barili F, Bloch KD, Bolger AF, Botker HE, Bozkurt B, Bugiardini R, Cannon C, de Lemos J, Eberli FR, Escobar E, Hlatky M, James S, Kern KB, Moliterno DJ, Mueller C, Neskovic AN, Pieske BM, Schulman SP, Storey RF, Taubert KA, Vranckx P, Wagner DR. Third universal definition of myocardial infarction. *J Am Coll Cardiol* 2012; **60**: 1581-1598 [PMID: 22958960 DOI: 10.1016/j.jacc.2012.08.001]

**Footnotes**

**Institutional review board statement:** The study was approved by the Ethics Committee of Shenzhen People’s Hospital (No. LL-KT-2014211) and conducted according to the Declaration of Helsinki.

**Clinical trial registration statement:** The trial was registered in Chinese Clinical Trial Registry on August 15, 2019 (ChiCTR1900025174) and is available at http://www.chictr.org.cn/showproj.aspx?proj=42063.

**Informed consent statement:** All study participants, or their legal guardian, provided informed written consent prior to study enrollment.

**Conflict-of-interest statement:** The authors declare that they have no conflict of interest.

**CONSORT 2010 Statement:** The authors have read the CONSORT 2010 Statement, and the manuscript was prepared and revised according to the CONSORT 2010 Statement.

**Open-Access:** This article is an open-access article that was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution NonCommercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: http://creativecommons.org/Licenses/by-nc/4.0/

**Manuscript source:** Unsolicited manuscript

**Peer-review started:** November 10, 2020

**First decision:** December 8, 2020

**Article in press:** December 27, 2020

**Specialty type:** Medicine, research and experimental

**Country/Territory of origin:** China

**Peer-review report’s scientific quality classification**

Grade A (Excellent): A

Grade B (Very good): B

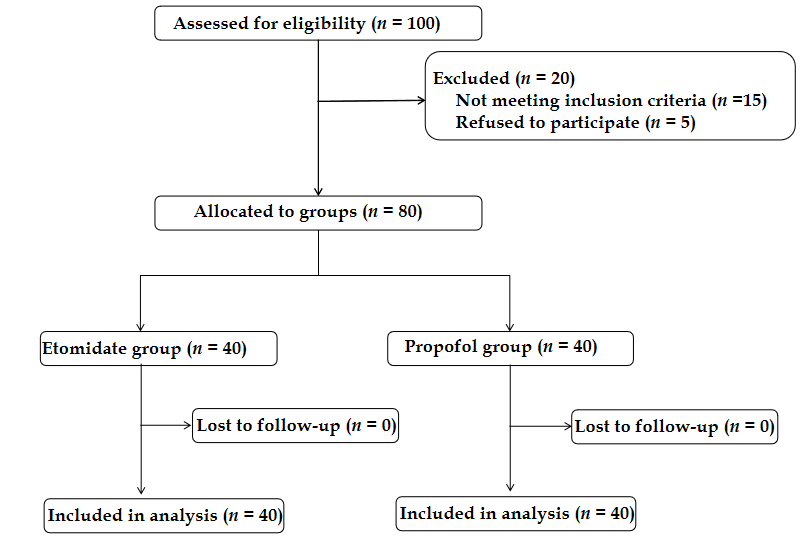
Grade C (Good): 0

Grade D (Fair): 0

Grade E (Poor): 0

**P-Reviewer:** Găman MA **S-Editor:** Fan JR **L-Editor:** Wang TQ **P-Editor:** Liu JH

**Figure Legends**



**Figure 1** **Flow chart of patient selection.**

**Table 1** **Baseline clinical characteristics of the study participants**

|  |  |  |  |
| --- | --- | --- | --- |
|  | **Propofol group (*n* = 40)** | **Etomidate group (*n* = 40)** | ***P* value** |
| Male sex, *n* (%) | 21 (52.5%) | 23 (57.5%) | 0.651 |
| Age (years), mean ± SD | 56.7 ± 6.6 | 53.6 ± 6.1 | 0.452 |
| Weight (kg), mean ± SD | 64.6 ± 12.5 | 66.4 ± 16.3 | 0.084 |
| Height (cm), mean ± SD | 165.7 ± 11.9 | 163.4 ± 13.3 | 0.732 |
| Type of surgery, *n* (%) |  |  |  |
| Gastrointestinal | 26 (65.0%) | 23 (57.5%) | 0.946 |
| Hepatobiliary | 8 (20.0%) | 10 (25.0%) | 0.783 |
| Thyroid | 6 (15.0%) | 7 (17.5%) | 0.562 |

SD: Standard deviation.

**Table 2 Incidences of cardiovascular events during anesthesia**

|  |  |  |  |
| --- | --- | --- | --- |
|  | **Propofol group (*n* = 40)** | **Etomidate group (*n* = 40)** | ***P* value** |
| Bradycardia, *n* (%) | 11 (27.5%) | 3 (7.5%) | 0.037 |
| Tachycardia, *n* (%) | 1 (2.5%) | 3 (7.5%) | 0.615 |
| Hypotension, *n* (%) | 17 (42.5%) | 4 (10.0%) | 0.027 |
| ST-T segment changes, *n* (%) | 8 (20.0%) | 2 (5.0%) | 0.029 |
| Ventricular premature beats, *n* (%) | 11 (27.5%) | 3 (7.5%) | 0.041 |

**Table 3 Comparison of hemodynamic parameters between groups**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  | **Before anesthesia induction** | **3 min after anesthetic injection** | **Just after tracheal intubation** | **3 min after tracheal intubation** | **5 min after tracheal intubation** |
| Heart rate (beats/min) |  |  |  |  |  |
| Propofol group | 82.6 ± 9.1 | 58.9 ± 7.1 | 66.5 ± 9.7 | 63.2 ± 6.7 | 68.9 ± 8.8 |
| Etomidate group | 79.0 ± 7.3 | 71.3 ± 9.3 | 76.5 ± 6.9 | 71.3 ± 6.4 | 76.8 ± 5.2 |
| *P* value | 0.223 | 0.012 | 0.044 | 0.253 | 0.072 |
| SBP (mmHg) |  |  |  |  |  |
| Propofol group | 132.7 ± 12.4 | 89.4 ± 16.3 | 100.2 ± 13.1 | 93.1 ± 17.4 | 103.8 ± 13.2 |
| Etomidate group | 129.6 ± 17.2 | 100.3 ± 19.3 | 117.5 ± 12.9 | 112.3 ± 16.4 | 121.5 ± 15.3 |
| *P* value | 0.813 | 0.041 | 0.112 | 0.214 | 0.712 |
| DBP (mmHg) |  |  |  |  |  |
| Propofol group | 76.7 ± 18.7 | 62.9 ± 16.3 | 72.1 ± 16.7 | 68.6 ± 17.2 | 70.9 ± 18.4 |
| Etomidate group | 79.0 ± 16.1 | 73.0 ± 16.4 | 90.8 ± 20.2 | 91.2 ± 16.3 | 82.2 ± 15.4 |
| *P* value | 0.60 | 0.009 | 0.008 | 0.02 | 0.01 |
| MAP (mmHg) |  |  |  |  |  |
| Propofol group | 92.6 ± 18.7 | 68.9 ± 16.1 | 76.5 ± 16.5 | 86.2 ± 18.2 | 80.8 ± 18.2 |
| Etomidate group | 95.1 ± 17.2 | 80.2 ± 16.7 | 96.3 ± 22.5 | 93.5 ± 16.4 | 89.8 ± 15.5 |
| *P* value | 0.69 | 0.007 | 0.043 | 0.012 | 0.018 |

Data are presented as the mean ± standard deviation (*n* = 40 in each group). DBP: Diastolic blood pressure; MAP: Mean arterial pressure; SBP: Systolic blood pressure.

**Table 4 Comparison of vasopressor use between groups**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | **Ephedrine use (mg)** | | **Phenylephrine use (μg)** | |
|  | **Induction** | **Maintenance** | **Induction** | **Maintenance** |
| Propofol group | 7.0 ± 1.6 | 9.8 ± 3.2 | 17.5 ± 3.8 | 15.1 ± 1.6 |
| Etomidate group | 3.1 ± 2.0 | 2.6 ± 1.1 | 6.2 ± 1.3 | 7.5 ± 2.1 |
| *P* value | < 0.001 | < 0.001 | < 0.001 | < 0.001 |

Data are presented as the mean ± standard deviation (*n* = 40 in each group).

**Table 5 Comparison of bispectral index values between groups**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  | **Before anesthesia induction** | **3 min after anesthetic injection** | **Just after tracheal intubation** | **3 min after tracheal intubation** | **5 min after tracheal intubation** |
| Propofol group | 97.0 ± 1.7 | 46.9 ± 2.1 | 47.5 ± 1.5 | 46.2 ± 1.2 | 46.8 ± 1.8 |
| Etomidate group | 97.4 ± 1.20 | 47.2 ± 1.7 | 46.5 ± 1.5 | 44.3 ± 1.4 | 45.0 ± 1.3 |
| *P* value | 0.91 | 0.29 | 0.38 | 0.32 | 0.43 |

Data are presented as the mean ± standard deviation (*n* = 40 in each group).



Published by **Baishideng Publishing Group Inc**

7041 Koll Center Parkway, Suite 160, Pleasanton, CA 94566, USA

**Telephone:** +1-925-3991568

**E-mail:** bpgoffice@wjgnet.com

**Help Desk:** https://www.f6publishing.com/helpdesk

https://www.wjgnet.com



**© 2021 Baishideng Publishing Group Inc. All rights reserved.**