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*Original Article*

# A comparison of the cardioprotective effect of esmolol, dexmedetomidine and lidocaine in elderly patients undergoing noncardiac surgery

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**Abstract:** Background: Previous studies have reported the cardioprotective effect of dexmedetomidine, esmolol and lidocaine. We compared the effect of dexmedetomidine, esmolol and lidocaine infusion on elderly patients undergoing noncardiac surgery. Methods: 384 elderly patients were enrolled. Esmolol (10-20 g/kg/min, n=90), dexmedetomidine (0.3-0.7 g/kg/h, n=86), lidocaine (1.5 mg/Kg/h, n=86) and saline (5 ml/h, n=92) were respectively infused in four groups prior to the induction of general anesthesia to the end of surgery. Perioperative electrocardiography, myocardial enzyme, cardiac function, intraoperative hemodynamics, and postoperative outcome of the four groups were compared. Results: Esmolol and dexmedetomidine can effectively inhibit hemodynamic fluctuations caused by noxious stimulation during anesthesia and surgery. Lidocaine can effectively inhibit the occurrence of premature ventricular contractions, while esmolol and dexmedetomidine may increase the incidence of atrioventricular block after non-cardiac surgery. All these agents can effectively inhibit the increase of myocardial injury markers and the incidence of myocardial ischemia immediately after non-cardiac surgery. Conclusion: The infusion of lidocaine, esmolol or dexmedetomidine has myocardial protection in elderly undergoing non-cardiac surgery. Lidocaine is more suitable for patients with ventricular arrhythmia. Esmolol and dexmedetomidine are more helpful in maintaining hemodynamic stability, but more caution should be payed to avoid the occurrence of atrioventricular block.

**Keywords:** Cardioprotective effect, esmolol, dexmedetomidine, lidocaine, elderly patients, noncardiac surgery

## Introduction

Increasing life expectancies paired with age-related comorbidities have resulted in the continued growth of the elderly surgical population. Studies have estimated that approximately 53% of all surgical procedures are performed on patients over the age of 65. Projections estimate that approximately half of the population over the age of 65 will require surgery once in their lives [1]. Perioperative stress, anxiety, fear and other psychological states, as well as afferent stimuli caused by trauma, surgery and anesthesia, make it more likely for elderly patients to have cardiac complications, such as myocardial ischemia [2, 3], which can induce significant changes in heart function, and even induce a series of adverse events, e.g. myocardial infarction and even death [4, 5].

The most common perioperative cardiac complications in the elderly are myocardial ischemia and ventricular arrhythmias. Intraoperative myocardial ischemia is an important predictor of postoperative adverse cardiac events, such as myocardial infarction and cardiac death, which happens at least 4 hours before cardiac events [6, 7]. Therefore, prevention of perioperative myocardial ischemia and ventricular arrhythmias in high-risk patients is pivotal to reduce the incidence of cardiac accidents and improve postoperative outcomes.

β-adrenergic antagonist esmolol, α-2 adrenergic agonist dexmedetomidine and lidocaine are commonly used cardiovascular agents during anesthesia, yet there remains controversy in their effects on the cardiac protection [8-12]. In order to provide a reference for the rational use of cardiovascular agents and myocardial protection strategies in elderly patients, we performed a prospective randomized controlled trial to evaluate the cardiac protection effect of esmolol, dexmedetomidine and lidocaine on elderly patients undergoing non-cardiac surgery, by comparing perioperative electrocardiography, myocardial enzyme, cardiac function, intraoperative hemodynamics, and postoperative outcome.

## Material and methods

### *Case selection and grouping*

This study was approved by the Ethics Committee of the Ruijin Hospital, Shanghai Jiao Tong University School of Medicine. All patients or their designated representatives were fully informed of the objectives of the study and the possible risks, and all signed the informed consent form. All patients maintained the right to terminate their participation in the study at any stage of the experiment.

After obtaining written informed consent from each patient, elderly patients of both genders undergoing gastrointestinal surgery with ASA I~II level and ages > 60 years were included. Patients who met one of the following criteria were excluded from the study: (1) emergency patients; (2) myocardial injury has been diagnosed before surgery; (3) patients with infectious fever or bacteremia, participating in other clinical trials within 3 months prior to enrollment in this study; (4) plasma or plasma substitute were used intraoperative; (5) hepatic or renal dysfunction; (6) abnormal coagulation function; (7) history of allergy to esmolol, dexmedetomidine or lidocaine. According to these criteria, a total of 384 patients were selected, all of which were randomly divided into four groups based on computer-generated codes that were maintained in sequentially numbered opaque envelopes: Esmolol group (group Es, n=98), Dexmeditomidine group (group Dex, n=92), Lidocaine group (group Lido, n=93) and Control group (n=101). During the experiment, additional cases were excluded due to the loss of follow-up.

### *Operation procedure*

*Method of anesthesia:* On the morning of surgery and before induction of anesthesia, the allocation envelope was opened by a nurse or anesthetist with no involvement in patient management. No preoperative medication was used. Once the patient was moved into the operating room, a Datex S/5 monitor (Absolute Medical Equipment, Stony Point, NY, USA) was used for noninvasive monitoring of blood pressure, electrocardiogram, pulse, and blood oxygen saturation. The depth of anesthesia was monitored by Narcotrend (MT MonitorTechnik GmbH & Co. KG D-24576 Bad Bramstedt). Intravenous infusion was established at the left forearm, and a single dose of midazolam 6-10 mg/kg was injected intravenously for sedation.

All patients received target-controlled infusion of propofol with the target plasma concentration of 4 μg/ml. After the consciousness of the patients disappeared, all the four groups were given intravenous injection of 2 μg/kg fentanyl and 0.6 mg/kg rocuronium bromide when NT index measured by Narcotrend was less than D2, and all underwent endotracheal intubation and anesthetic equipment connection for mechanical ventilation with oxygen flow rate of 2 L/min to maintain PETCO2 at 35~40 mmHg (1 mmHg =0.133 kPa). During the operation, intravenous administration of propofol TCI (2.5-3.5 μg/ml) and inhalation of sevoflurane 0.6 MAC were combined to maintain anesthesia, and intermittent intravenous injection of fentanyl 2-4 μg/kg and vecuronium 0.3 mg/kg were given, based on the surgical process to maintain NT between D2-E1. Plasma, plasma substitute or cell saver were used intra-operative to maintain Hb > 70 g/L. At the end of the operation, the patient's intraoperative blood loss, urine amount, and total operation duration were recorded.

*The administration of cardiovascular agents:* Esmolol (10-20 mg/kg/min), dexmedetomidine (0.3-0.7 mg/kg/h), lidocaine (1.5 mg/Kg/h) and saline (5 ml/h) were respectively infused in four groups prior to the induction, to maintain the heart rate > 50 bp/min and mean arterial pressure (MAP) within 20% of the baseline value, until the end of surgery. A 10 mg bolus of ephedrine was administered when MAP < 60 mmHg. A 0.5 mg bolus of atropine was administered when HR < 50 bp/min.

*Data collection:* The blood pressure and heart rate were collected at the following time points: entering the operation room (T0), prior to the

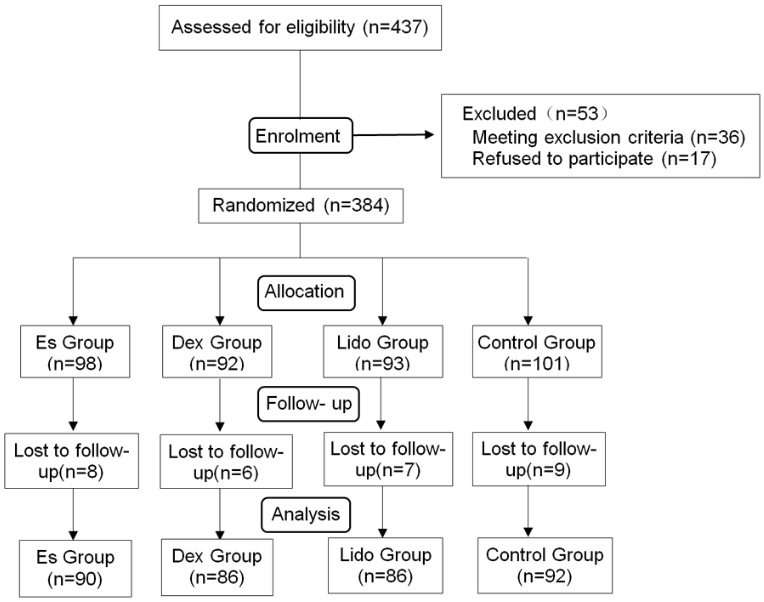


**Figure 1.** CONSORT diagram for the study.

induction (T1), at the end of induction (T2), after endotracheal intubation (T3), prior to incision (T4), after incision (T5), prior to exploring the abdominal cavity (T6), after exploring the abdominal cavity (T7), the end of surgery (T8), prior to extubation (T9), 3 min after extubation (T10).

The portable electrocardiogram recording box (CM1, CM3, and CM5 three-channel, MGY-H12, USA) was used to record the patients' ECG for 24 hours preoperative and postoperative. Acute ischemia/infarction was diagnosed from ECG according to "2009 AHA/ACCF/HRS Recommendations for the Standardization and Interpretation of the Electrocardiogram" [13].

Serum concentrations of the cardiac enzymes TnI, cardiac myoglobin and N-terminal pro-brain natriuretic precursor (NT-proBNP) were measured before operation, at the end of operation and 24, 48 h after surgery using BECKMAN COULTER Access 2 System (Beckman Coulter, USA), based on a direct chemiluminescence method.

We recorded length of ICU and hospital stay, postoperative adverse events, and death from any cause within one year of surgery.

*Statistical analysis*

The experimental data were analyzed by SPSS 20.0 software (IBM, Armonk, NY, USA), and the normally distributed measurement data were presented as mean ± SD. One-way ANOVA was used for the comparisons of the measurement data between groups, and the LSD method was used for pairwise comparisons. Chi-square test was used for comparing the difference of count data between groups. A $P$ value < 0.05 was considered to be statistically significant.

## Results

From July 1, 2015, to December 30, 2016, a total of 437 elderly patients undergoing elective non-cardiac surgery (gastrointestinal surgery) were screened for eligibility, with 384 patients consenting to participate in the study and randomized to intervention or control (**Figure 1**). 30 of these patients were excluded due to loss of follow-up. Thus, 90 patients receiving esmolol, 86 patients receiving dexmedetomidine, 86 patients receiving lidocaine and 92 patients receiving saline were evaluated.

The characteristics of the four patient groups were similar, including gender, age, surgery duration, crystalloid volume, colloid volume, the length of ICU stay, the length of hospital stay after operation and 1-year survival rate (**Table 1**).

*Continuous infusion of esmolol or dexmedetomidine can effectively inhibit hemodynamic fluctuations caused by noxious stimulation during anesthesia and surgery*

As shown in **Figure 2**, blood pressure was significantly increased in each group after intubation (T3) compared to blood pressure at the end of induction (T2), $P < 0.05$. The heart rate of the control group and the lidocaine group was significantly increased after intubation (T3) compared to T2 ($P < 0.05$), while the esmolol and dexmedetomidine groups did not show significant increase in heart rate after intubation ($P > 0.05$). In addition, after intubation (T3), the heart rate of the esmolol group and the dexmedetomidine group was slower than that of the

**Table 1.** Patient characteristics. Data are expressed as number of patients and mean (SD)

| Group | Gender M/F | Age (y) | Surgery duration (min) | Crystalloid (mL) | Colloid (mL) | ICU stay (d) | Hospital stay (d) | 1-year survival rate (%) Gastric cancer | 1-year survival rate (%) Intestinal cancer |
|---|---|---|---|---|---|---|---|---|---|
| Control | 48/42 | 66±5 | 160±27 | 1608±226 | 795±216 | 1±1 | 13±2 | 48.05 | 70.41 |
| Esmolol | 44/42 | 66±5 | 168±37 | 1708±196 | 833±301 | 2±1 | 15±2 | 50.43 | 68.53 |
| Dexmede-tomidine | 42/44 | 66±5 | 170±36 | 1644±271 | 779±285 | 2±1 | 15±2 | 51.02 | 67.77 |
| Lidocaine | 49/43 | 66±5 | 172±35 | 1532±305 | 863±197 | 1±1 | 14±1 | 47.88 | 71.11 |

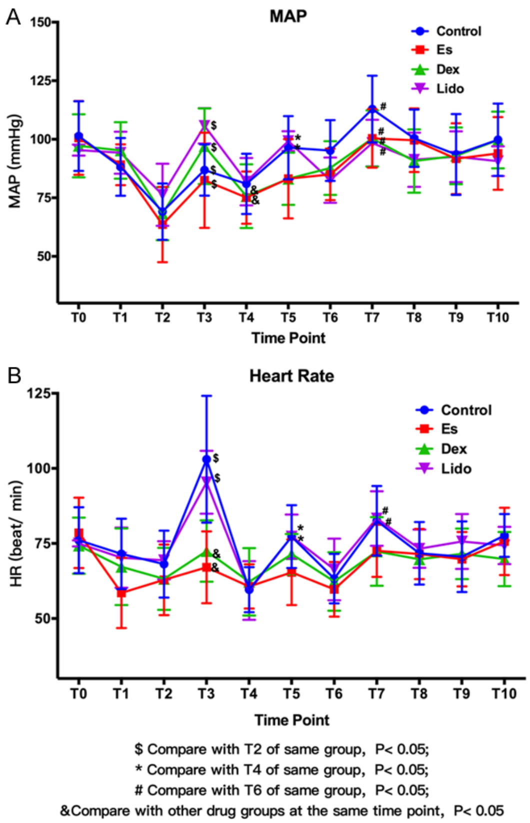


**Figure 2.** The hemodynamic change in four groups of patients at different time points: entering the operation room (T0), prior to the induction (T1), at the end of induction (T2), after endotracheal intubation (T3), prior to incision (T4), after incision (T5), prior to exploring the abdominal cavity (T6), after exploring the abdominal cavity (T7), the end of surgery (T8), prior to extubation (T9), 3 min after extubation (T10).

control group (P < 0.05), while there was no significant difference in heart rate between the lidocaine group and the control group, indicating that continuous infusion of esmolol or dexmedetomidine from the beginning of anesthesia can effectively suppress the heart rate acceleration caused by intubation, which is not obvious in blood pressure control. Lidocaine has no effect on hemodynamic fluctuations due to intubation. Similar effect of esmolol and dexmedetomidine on hemodynamic fluctuations was observed after abdominal cavity exploration (T7).

The MAP of the esmolol group and the dexmedetomidine group before incision (T4) was significantly lower than that of the control group at the same time point (P < 0.05) (**Figure 2**), suggesting that attention should be paid to patients' blood pressure when there is less noxious stimulation if esmolol and dexmedetomidine were infused, and the time between incision and intubation should be shortened to prevent the occurrence of hypotension. Blood pressure and heart rate were significantly higher after incision (T5) than that before incision (T4) in control group and lidocaine group (P < 0.05), while no significant increases of blood pressure and heart rate were observed in esmolol group and dexmedetomidine group after incision (P > 0.05, **Figure 2**), indicating that infusion of esmolol or dexmedetomidine from the induction of anesthesia can effectively inhibit the heart rate and blood pressure increase caused by the incision, and lidocaine has no obvious effect on hemodynamic fluctuations due to incision.

The above results suggest that continuous infusion of esmolol or dexmedetomidine from the induction of anesthesia can effectively inhibit hemodynamic fluctuations caused by noxious stimulation during anesthesia and surgery during non-cardiac surgery in elderly patients, especially the increase of heart rate. Lidocaine has no such effect.

*Continuous infusion of esmolol, dexmedetomidine or lidocaine from anesthesia induction can effectively inhibit the increase of myocardial injury markers*

The concentrations of NT-proBNP, Myo, and cTNI in the four groups were within the normal range before surgery, and there was no significant difference (**Figure 3**). The concentra-

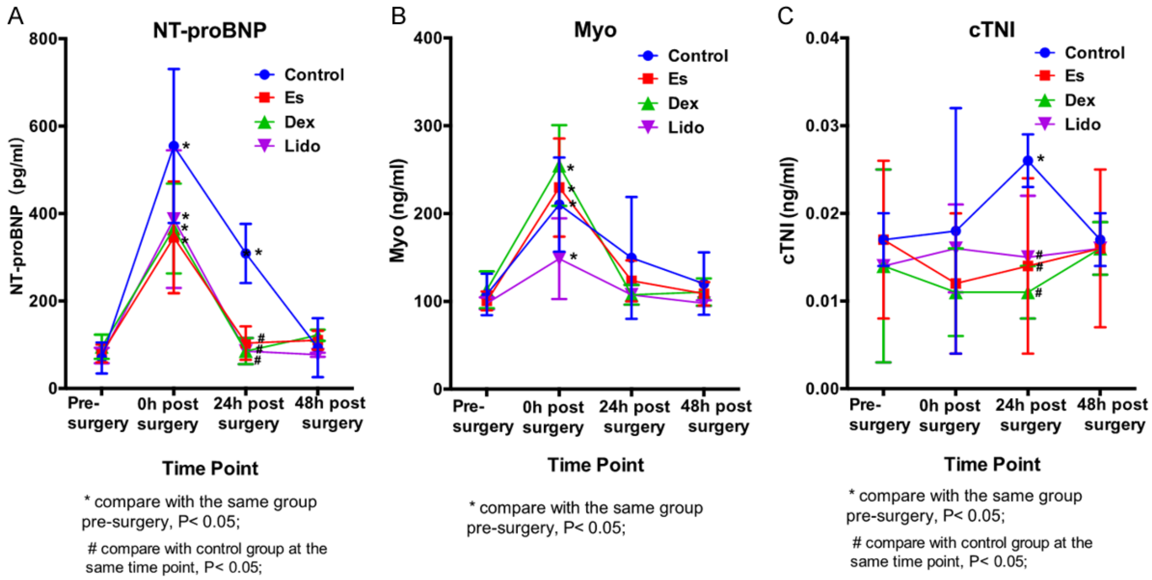


**Figure 3.** The change in myocardial injury markers in four groups of patients.

tions of Myo and NT-proBNP were significantly increased in the four groups at the end of the operation (P < 0.05), and the concentration of cTNI did not change significantly. In addition, the concentration of NT-proBNP in the three drug groups was lower than that in the control group at the end of surgery (P < 0.05). 24 h after surgery, the concentration of NT- proBNP and cTnI in control group is still significantly higher than that before surgery (P < 0.05), which is much lower in three drug groups, with no difference compared to that before surgery in the same group. The concentration of NT-proBNP, Myo, and cTNI in all four experimental groups returned to preoperative levels 48 h after surgery.

The above results suggest that continuous infusion of esmolol, dexmedetomidine or lidocaine from anesthesia induction can effectively inhibit the increase of myocardial injury markers in elderly patients after non-cardiac surgery.

*Continuous infusion of lidocaine from the induction of anesthesia can effectively inhibit the occurrence of premature ventricular contractions*

As shown in **Figure 4A**, the incidence of preoperative ventricular premature beats was similar in the four groups of patients, which did not change significantly 24 h after surgery in control group, esmolol group and dexmedetomidine group (P > 0.05). In lidocaine group, the incidence of premature ventricular contractions (2.17%) was not only significantly lower than that before surgery (13.04%), but also significantly lower than the other three groups 24 h after operation. The difference was statistically significant (P < 0.05).

As shown in **Figure 4B**, there was no significant difference in the incidence of atrial fibrillation among the four groups, both preoperatively and postoperatively (P > 0.05), from 7% to 12%.

As shown in **Figure 4C**, no atrioventricular block was found in the four groups of patients during preoperative electrocardiography. The incidence of atrioventricular block after surgery in the esmolol group and dexmedetomidine group was 10.47%, which was not only significantly higher than that before surgery, but also significantly higher than control group (1.96%) and the lidocaine group (2.17%) (P < 0.05).

The above results suggest that infusion of lidocaine from the induction of anesthesia can effectively inhibit the occurrence of premature ventricular contractions in elderly patients after non-cardiac surgery, while esmolol and dexmedetomidine have no such effect. Esmolol and dexmedetomidine may increase the incidence of atrioventricular block after non-cardiac surgery in elderly patients.

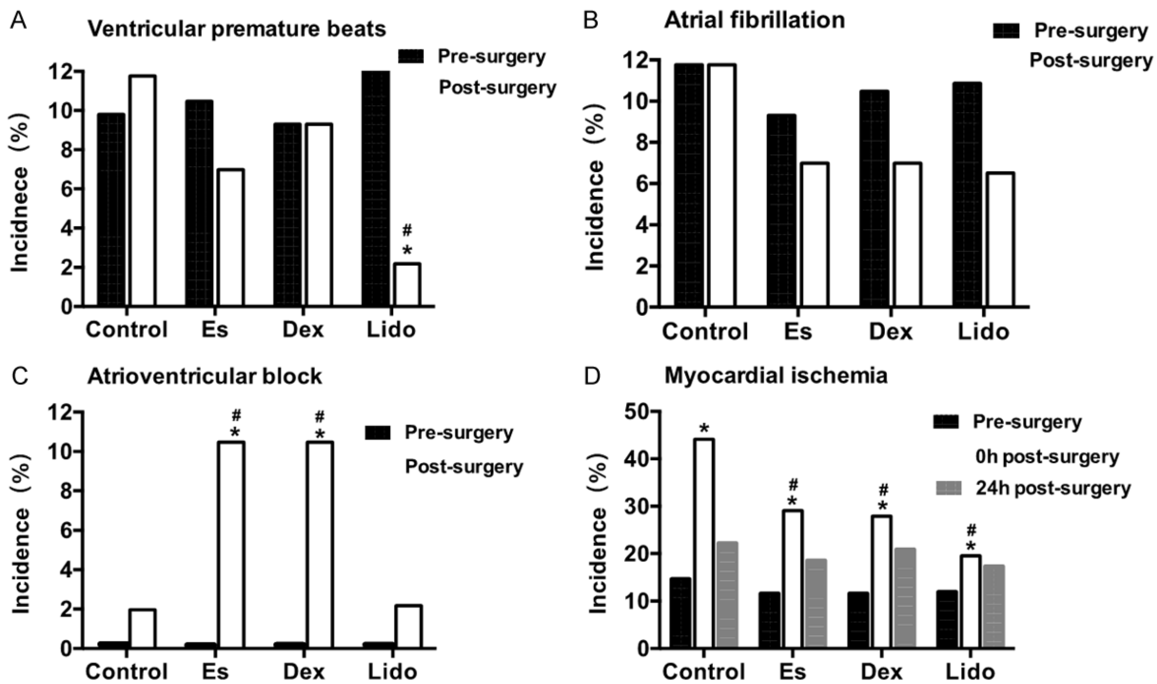


**Figure 4.** Arrhythmias and myocardial ischemia in different groups of patients before and after operation. A. $^*$compare with the same group pre-surgery, P < 0.05; $^\#$compare with other three groups at the same time point, P < 0.05; B. There was no significant difference in the incidence of atrial fibrillation among the four groups, both preoperatively and postoperatively (P > 0.05). C. $^*$compare with the same group pre-surgery, P < 0.05; $^\#$compare with control group and lidocaine group at the same time point; D. $^*$compare with the same group pre-surgery, P < 0.05; $^\#$compare with control group at the same time point.

*Continuous infusion of esmolol, dexmedetomidine or lidocaine can effectively inhibit the incidence of myocardial ischemia immediately after non-cardiac surgery*

As shown in **Figure 4D**, the incidence of preoperative myocardial ischemia was similar in the four groups of patients, approximately 12%, which was significantly increased in each group after surgery (P < 0.05): the control group was 44.12%, the esmolol group was 29.07%, and the dexmedetomidine group was 27.91%, the lidocaine group was 19.57%. In addition, the incidence in control group was significantly higher than that of the three drug groups (P < 0.05). At 24 h after surgery, the incidence of myocardial ischemia in the four groups was decreased to about 20%. This indicates that continuous infusion of esmolol, dexmedetomidine or lidocaine can effectively inhibit the incidence of myocardial ischemia immediately after non-cardiac surgery in elderly patients.

## Discussion

In this prospective randomized controlled trial, we compared the effect of esmolol (10-20 mg/kg/min), dexmedetomidine (0.3-0.7 mg/kg/h) and lidocaine (1.5 mg/Kg/h) infusion from induction of anesthesia on intraoperative hemodynamics, myocardial injury outcome in elderly patients undergoing non-cardiac surgery, and found that esmolol, dexmedetomidine but not lidocaine can effectively Inhibit hemodynamic fluctuations caused by noxious stimuli, especially heart rate. Lidocaine, but not esmolol and dexmedetomidine, can effectively inhibit the occurrence of postoperative ventricular premature beats and atrioventricular block. All three drugs can effectively inhibit the increase in post-myocardial enzymes and the incidence of myocardial ischemia after surgery. The three drugs have no significant effect on the operation duration, intraoperative fluid volume, hospital stay, ICU stay time and one-year survival rate in elderly patients.

Although many animal studies [14, 15] have confirmed that dexmedetomidine can protect organs including the heart by inhibiting central sympathetic signaling and inhibiting ischemia-reperfusion injury and anti-inflammation, however, the results of clinical studies are controversial. Jalonen [16] found that dexmedetomidine can reduce surgical stress by decreasing plasma catecholamine level, and improve one-year survival rate after surgery [17]. The study by Kim [11] and Tosun [18] did not find that dexmedetomidine has a myocardial protective effect on patients in surgery. The possible reason is that these studies used remifentanil and isoflurane for anesthesia maintenance, and many clinical studies have confirmed that remifentanil and isoflurane can reduce myocardial injury markers in patients with surgery, and have myocardial protective effects [19-21], so it is probably that remifentanil and isoflurane masked the myocardial protection of dexmedetomidine.

Lidocaine is a commonly used local anesthetic and antiarrhythmic drug in clinical practice, but recently, more and more studies have found that its role in myocardial protection cannot be underestimated. Lidocaine can reduce myocardial $Na^+$ channel, reduce $Na^+$-$Ca^{2+}$ exchange, reduce $Ca^{2+}$ load in cardiomyocytes, reduce ROS production, and improve mitochondrial function, thereby exerting myocardial protection against ischemia-reperfusion injury [22, 23]. Previous animal experiments [24, 25] and clinical studies [11, 12] confirmed the myocardial protection of lidocaine. The results of this study are consistent with previous reports. Lidocaine did not help keeping hemodynamic stability during surgery compared with esmolol and dexmedetomidine, but the incidence of postoperative ventricular premature beats in the lidocaine group was significantly lower than that before surgery and did not induced atrioventricular block, suggesting that lidocaine can be given priority in elderly surgical patients with arrhythmia.

Esmolol is a highly selective and most commonly used b1 receptor blocker. Perioperative use of esmolol has myocardial protection, mainly because it slows heart rate (increased myocardial relaxation time and perfusion), reduces myocardial contractility (reduces oxygen consumption). In addition, esmolol can also inhibit lipolysis and reduce the amount of free fatty acids in the circulation, thereby exerting anti-arrhythmia effects, especially in acute myocardial ischemia [26]. Intraoperative use of b1 receptor blocker can reduce the use of analgesics in non-cardiac surgery in elderly patients, improve intraoperative hemodynamic stability and anesthesia recovery [27, 28], and reduce the risk of the incidence and mortality of cardiac complications during surgery [29]. However, β1-blockers also have some side effects, such as sinus bradycardia, negative inotropic effects, and increased risk of cerebrovascular accidents [8, 30]. Our study also found that continuous pumping of esmolol and dexmedetomidine prior to induction of anesthesia may increase the incidence of atrioventricular block after non-cardiac surgery in elderly patients, suggesting that in elderly patients with atrioventricular block, esmolol and dexmedetomidine should be avoided during surgery, especially dexmedetomidine, because its terminal elimination half-life ($t_{1/2}$=2 h) [31] is longer than esmolol ($t_{1/2}$=9 min).

In acute myocardial ischemia, the level of Myo in serum rises first and has certain advantages in terms of time. However, the specificity of Myo is relatively low, so other markers need to be combined in clinical diagnosis. The concentration of troponin is very low in healthy human blood and it lasts for longest time compared to other markers, so it is becoming the "gold standard" for the diagnosis of acute myocardial ischemia. The present study selected troponin I (cTnI) because it exists only in the myocardium, and the peak appears early, with higher specificity and sensitivity. However, in practice, we found that extreme values detecting cTnI, which influenced the stability of the experiment, so we also evaluated NT-proBNP. The greater the range of myocardial ischemia and the more severe the degree of ischemia, the higher NT-proBNP level and faster the rate of increase, so NT-proBNP level can reflect the severity of acute myocardial infarction patients [32, 33]. Three myocardial enzymes were combined to prove that esmolol, dexmedetomidine and lidocaine can effectively inhibit the incidence of myocardial ischemia immediately after non-cardiac surgery in elderly patients.

Although the present study found that esmolol, dexmedetomidine and lidocaine have cardioprotective effects, the prognostic indicators of the three groups, such as ICU stay days, hospital days and one-year survival rate, did not differ from control group, indicating that larger sample size is probably needed in the future to further explore the impact of these three drugs on outcome of surgical patients.

To conclude, the infusion of lidocaine, esmolol or dexmedetomidine has myocardial protection in elderly undergoing non-cardiac surgery. Lidocaine is more suitable for patients with ventricular arrhythmia. Esmolol and dexmedetomidine are more helpful in maintaining hemodynamic stability, but more caution should be payed to avoid the occurrence of atrioventricular block.

## Disclosure of conflict of interest

None.

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