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The effect of continuous perfusion of esmolol on cardiovascular risk in elderly patients undergoing noncardiac surgery

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We evaluated the effect of continuous perfusion of esmolol on cardiovascular risk during curative laparoscopic surgery for gastrointestinal cancer in elderly patients. Sixty patients with gastrointestinal cancer, aged from 60 to 80 years, were divided into an esmolol group (ES, n = 30) and a control group (NS, n = 30). ES patients were treated with esmolol at a dose of 0.3 mg/kg 3 min before tracheal intubation, and received continuous perfusion of esmolol at a dose of 50 µg/kg/min during operation. In NS, esmolol was replaced by saline. SBP/DBP, MAP, HR, S_PO_2, $P_{ET}CO_2$, the depth of anesthesia and the value of RPP were recorded before anesthesia (T_0), during intubation (T_1), 10 min before pneumoperitoneum (T_2), during pneumoperitoneum (T_3), 30 min after incision (T_4), at the end of surgery (T_5), during extubation (T_6) and 30 min after extubation (T_7). The serum levels of cTnI, CK, CK-MB and LDH were measured before anesthesia, 6 and 30 h after surgery. HR, MAP, RPP at T_1, T_3, T_6 in ES were obviously decreased compared with NS ($P < 0.05$). There were no significant differences between both groups at different time points with respects to the serum levels of cTnI, CK, CK-MB and LDH. No major adverse cardiocerebral event was observed in both groups in three postoperative months. The present study indicated that the application of esmolol during curative laparoscopic surgery for gastrointestinal cancer can effectively reduce the cardiovascular responses in intubation, operation and extubation, sustain hemodynamic stable, reduce myocardial oxygen consumption, and prevent perioperative adverse cardiovascular events, but had no significant myocardial protective effect.

1. Introduction

The number of surgical treatments of elderly patient population is increasing. Cardiovascular events during noncardiac operations in this patient population occur frequently and place them at high risk of morbidity and mortality (Mangano 1996; Sanders et al. 2009). The appropriate perioperative management measures are badly in need in clinic.

Beta-blockers are among the most common drugs in the treatment of cardiovascular diseases. However, there is a controversy about the perioperative use of β-blockers in noncardiac surgery (Stern and Cifu 2015). Some studies showed that there were benefits with β-blockers in perioperative patients, such as reducing the incidence of myocardial ischemia during mild hypertension patients, reducing mortality and the incidence of cardiovascular complications for patients who have or are at risk for coronary artery disease undergoing noncardiac surgery, reducing the perioperative incidence of death from cardiac causes and nonfatal myocardial infarction in high-risk patients who are undergoing major vascular surgery. On the other hands, some studies indicated negative effects or ineffectiveness of perioperative β-blockers. For example, Devereaux et al. found that fewer patients in the metoprolol group than in the placebo group reached the primary endpoint and had a myocardial infarction, and there were more deaths in the metoprolol group. Besides, more patients in the metoprolol group had a stroke than in the placebo group (Devereaux et al. 2008). Yang et al. (2006) showed that metoprolol was not effective in reducing 30-day and 6-month postoperative cardiac event rates. Therefore, the perioperative application of β-blockers in noncardiac surgery may need further clarification.

Esmolol is one of the selective ultrashort-acting β_1-blockers, possessing the effects of slowing down the heart rate and lowering blood pressure. Previous studies have reported the application of esmolol in coronary bypass operation (Kuhn et al. 1999). However, its effect on cardiovascular risk in elderly patients undergoing noncardiac surgery is unclear.

This present study investigated the effect of a continuous perfusion of esmolol on cardiovascular risk during curative laparoscopic surgery for gastrointestinal cancer in elderly patients, through observing the effect of esmolol on the serum levels of BNP, LDH, CK, CK-MB, cTnI and the changes of hemodynamics.

2. Investigations and results

The male/female ratio, age, weight, ASA grading and time of operation did not differ significantly between both groups ($P > 0.05$) (Table 1).

Table 1: Comparison of general index between ES and NS group

	ES Group	NS Group
No. of patients	30	30
Male female ratio	18/12	17/13
Age	69.3±5.4	66.1±12.5
Weight (kg)	60.7±6.7	60.3±7.2
ASA I/II	17/13	19/11
Operation time (min)	180.5±16.5	180.3±18.2

Intra-group comparison results showed: In ES group, comparing with T_0, the values of HR at T_1-T_5 decreased significantly ($P < 0.05$). MAP at T_1-T_7 decreased significantly ($P < 0.05$). RPP at T_1-T_5, and T_7 decreased significantly ($P < 0.05$). In NS group, comparing

Table 2: Hemodynamics and RPP data comparison at each time point between both groups

Time	HR(1/min)		MAP(mmHg)		RPP	
	ES	NS	ES	NS	ES	NS
T_0	76.8±6.5	73.7±8.2	92.7±7.7	95.9±6.4	10760±1564	10732±1927
T_1	71.3±6.7[bc]	81.9±4.7[a]	84.2±6.9[bc]	94.6±6.9	8115±962[bc]	12240±1043[a]
T_2	68.9±7.3[b]	68.3±7.1[b]	83.9±8.1[b]	86.0±4.9[b]	8162±1212[b]	8576±1089[b]
T_3	69.2±7.2[bc]	81.9±4.7[a]	85.5±6.3[bc]	95.5±4.7	8535±1096[bc]	11736±991[a]
T_4	66.0±6.6[b]	65.5±5.7[b]	84.0±8.2[b]	86.0±13.3[b]	7834±1208[b]	8276±1174[b]
T_5	68.0±6.1[b]	69.5±6.9[b]	85.7±6.9[b]	88.2±7.2[b]	8697±1014[b]	9072±1332[b]
T_6	79.5±7.0[c]	86.2±4.4[a]	84.9±7.1[bc]	95.4±7.0	10161±1316[c]	13093±1361[a]
T_7	74.3±4.9	72.7±6.5	86.1±4.6[b]	87.5±6.0[b]	9469±784[b]	9182±1110[b]

[a] means the values increased significantly comparing with T_0 ($P < 0.05$).
[b] means the values decreased significantly comparing with T_0 ($P < 0.05$).
[c] means the values decreased significantly comparing among groups ($P < 0.05$).

Table 3: Serum levels of cTnI, CK, CK-MB, LDH at each time points comparison

	ES group			NS group		
	Before anesthesia	6 h after operation	30 h after operation	Before anesthesia	6 h after operation	30 h after operation
cTnI (mg/L)	0.103±0.17	0.101±0.18	0.103±0.20	0.082±0.30	0.073±0.03	0.073±0.03
CK (U/L)	127.3±39.3	126.1±30.2	135.1±31.0	111.3±40.0	121.4±46.4	134.8±56.4
CK-MB (U/L)	12.1±4.2	12.3±4.0	13.9±5.2	11.9±5.4	12.5±4.9	13.0±4.9
LDH (U/L)	185.0±64.2	191.7±53.8	182.6±65.6	178.6±63.7	168.2±42.3	172.5±44.9

with T_0, HR values at T_1, T_3, T_6 increased significantly ($P < 0.05$), nevertheless the HR values at T_2, T_4, T_5 decreased significantly ($P < 0.05$). MAP at T_2, T_3, T_6 increased, but the increasing did not have statistical significance ($P > 0.05$). MAP at T_2, T_4, T_5, T_7 decreased significantly ($P < 0.05$). RPP at T_1, T_3, T_6 increased significantly ($P < 0.05$), at T_2, T_4, T_5, T_7 decreased significantly ($P < 0.05$). Comparison among groups: The HR, MAP, RPP values at T_1, T_3, T_6 in ES group decreased significantly ($P < 0.05$). These results can be seen in Table 2.

The differences of serum levels of cTnI, CK, CK-MB, LDH between both groups were insignificant ($P > 0.05$) (Table 3).

All patients were followed up 3 months after operation, no cardiocerebral event case was recurred.

3. Discussion

Senile patients are a special population which is often associated with organ hypofunction. Although some gerontal cardiovascular system has not led to disease, physiological aging, leads to an elevated perioperative incidence of related complications and an increase in mortality rate. Surgical stress responses lead to activation of the sympathetic nervous system, acting on cardiac muscle and blood vessel with the results of hypertension, tachycardia and possibly arrhythmia, increasing myocardial oxygen consumption, finally resulting in myocardial ischemia in elderly patients (Kim et al. 2015). Myocardial ischemia may cause ischemic injury, heart pump function, and induce arrhythmia or myocardial infarction. Therefore, myocardial ischemia is a severe cardiac risk event during surgery (Mangano et al. 1990), and it is very important to seek perioperative myocardial protection measures. Management of cardiovascular function through stabling hemodynamics and adjusting the rhythm of the heart can reduce the incidence of related complications and perioperative mortality rate of perioperation (Ackland and Gareth 2015).

Esmolol can reduce changes of heart rate and blood pressure caused by laryngendoscopy, tracheal intubation and extubation and operative wound, and reduces myocardial oxygen consumption during operation (Zangrillo et al. 2009). Its effects on unstable angina pectoris, myocardial ischemia, supraventricular arrhythmia, intraoperative and postoperative tachycardia and hypertension, and electric shock have been confirmed (Wiest and Haney 2012). Esmolol restrains β_1 receptor by competing catecholamine binding sites in the myocardium, to extend myocardial diastolic, control ventricular rate, slow the heart rate efficiently, reduce myocardial oxygen consumption, improve myocardial blood flow and oxygen consumption (Morelli et al. 2013; Wiest and Haney 2012). It can prevent and treat cardiovascular side effects produced by the rising of serum catecholamine concentration, and hence protect the cardiac muscle. Besides, esmolol can effectively control arrhythmia, stable haemodynamics and reduce the risk of related complications (Garnock-Jones 2012). Our study showed that esmolol can decrease the variation of blood pressure and heart rate significantly, reduce myocardial oxygen consumption to protect myocardial ischemia, which was consistent with previous studies.

Myocardial ischemia injury is a gradual process, including two phases. The first phase is the mild ischemia period. The energy supply and demand of myocardial cells is imbalanced during the first phase (Durdu et al. 2012). The second phase is severe ischemia period. The structure and form of myocardial cells were broken in this phase (Schurr et al. 2001). Various kinds of proteins released after myocardial necrosis, such as troponin (cTnI), creatine kinase (CK), and lactic dehydrogenase (LDH). The cTnI and CK-MB could reflect the degree of myocardial injury (Biccard and Rodseth 2010; Morita 2012). Myocardial infarction may happen after severe myocardial ischemia. Myocardial damage can be diagnosed by monitoring the cTnI (Chong et al. 2011), and this diagnostic method has been widely used. A large number of clinical studies in the recent 30 years demonstrated that CK-MB, with dominance sensitivity and specificity, is acknowledged as the gold-standard to diagnose acute cardiac injury. When myocardial ischemia and oxygen deficit to generate degeneration or necrosis occur, cardiac troponin I (cTnI) in cytoplasm quickly enters the blood circulation, so the serum level of cTnI is raised in 3-8 h. Therefore, cTnI is the most sensitive indicator to diagnose myocardial damage at present (Apak et al. 2005; Fernandes et al. 1999). Consequently, simultaneous determining the myocardial enzyme levels of LDH, CK, CK-MB and serum level of cTnI can reflect the degree of myocardial injury. Continuous infusion of esmolol could significant decrease the cTnI, CK and CK-MB of patients with ST-elevation acute myocardial infarction (Er et al. 2016). The present study showed that there was no obvious impact on the serum levels of cTnI, CK, CK-MB and LDH in elderly patients undergoing noncardiac surgery by continuous infusion of esmolol at a dose of 50 μg/kg/min, indicating no obvious cardioprotective effect of esmolol in this case.

In conclusion, elderly patients with cardiovascular regulating hypofunction have less adaption and compensation capacity to deal with the changes of circulatory system under stringent state. Tracheal intubation, extubation and CO_2 pneumoperitoneum may induce hyperfunction of the sympatheticadrenal system, followed by an increase of catecholamine release, resulting in accelerating heart rate, myocardial contraction strengthening, increasing myocardial oxygen demand. Intra-operative continuous perfusion of esmolol could stable haemodynamics, reduce myocardial oxygen consumption, and prevent perioperative cardiovascular adverse events. However, there is no obvious cardioprotective effect on elderly patients undergoing noncardiac surgery.

4. Experimental

4.1. Patients

The study was approved by Ethics Committee of the First Affiliated Hospital of Nanchang University and the signed informed consent was obtained from each patient. Sixty patients undergoing curative laparoscopic surgery for gastrointestinal cancer, 35 male patients and 25 female patients, aged from 60 to 80 years, ASA I or II, body weight 40-80 kg, were randomly divided into esmolol group (ES, n = 30) and control group (NS, n = 30). Exclusion criteria: sinus bradycardia, above I grade atrioventricular block, cardiogenic shock, obvious cardiac failure, bronchial asthma, serious chronic obstructive pulmonary disease, refractory cardiac insufficiency, and allergic to esmolol.

4.2. Anesthesia

All 60 patients had no preoperative medication. After transporting to the operating area, peripheral vein was opened and invasive blood pressure after puncturing the left radial artery under local anesthesia was monitored. ECG, HR, RR, S_PO_2, $P_{ET}CO_2$ were routine monitored. General anesthesia was induced by midazolam at 0.05 mg/kg body weight, sufentanil at 0.4-0.5 μg/kg body weight, rocuronium bromide at 0.6-1.0 mg/kg body weight, propofol at 1.0-1.5 mg/kg body weight. After inserting a tracheal cannula, mechanical ventilation was applied. Esmolol was injected in the ES group with 0.3 mg/kg body weight 3 min before the tracheal cannula was applied. The equal volume of normal saline was injected in the NS group. General anesthesia was maintained by continuous infusion of propofol at 3-8 mg/kg/h, cisatracurium at 1.0-2.0 mg/kg/h, intermittent infusion of sufentanil in both groups. Twenty and ten minutes before the operation finished, cisatracurium and propofol infusion was stopped, respectively. Continuous infusion of esmolol (50 μg/kg/min) was applied in the ES group until tracheal extubation. Depth of anesthesia was maintained at 40-60, $P_{ET}CO_2$ was maintained at 35-40 during the operation. Anesthesia recovery: Postoperative patients were sent to PACU to wake up. After recovering spontaneous breathing, all patients received neostigmine (0.5 mg/kg body weight), atropine (0.02-0.03 mg/kg body weight). The tracheal catheter was pulled out as the patients were sober. When patients' blood pressure was lower than the basic value of 70%, 2 mg dopamine was injected, when the HR was lower than 50 times/min, 0.5 mg atropine was injected, and this case will be weeded out.

4.3. Observation indexes

SBP/DBP, MAP, HR, S_PO_2, $PETCO_2$, the depth of anesthesia and the value of RPP (RPP=SBP*HR) were recorded before anesthesia (T_0), during intubation (T_1), 10 min before pneumoperitoneum (T_2), during pneumoperitoneum (T_3), 30 min after incision (T_4), the end of surgery (T_5), during extubation (T_6) and 30 min after extubation (T_7). Five milliliters of venous blood were taken before anesthesia induction, 6 and 30 h after operation. The blood samples were centrifuged at the rate of 4000 r/min for 10 min. Then the serum samples were taken into 1.5 mL EP tube and restored at –80 °C. The serum concentration of cardiac troponin I (cTnI) was measured by ELISA, the serum levels of creatine kinase (CK), creatine kinase-MB (CK-MB) and lactic dehydrogenase (LDH) were measured by immunochemiluminescence method. The adverse events were recorded in both groups during 3-month post-operation following up.

4.4. Statistical analysis

Data are presented as mean±SD. Data analyses were performed by using one-way analysis of variance (ANOVA) and *T* test on SPSS 17.0 software. Enumeration data were performed by *X2* test. Statistical significance was assumed for $P < 0.05$.

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Conflicts of interest: None declared

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