

Original Article

Analysis of esmolol and landiolol on elderly patients in the perioperative period with gastric surgery

Xianhui Yang¹, Shumin Li²

¹The Second Affiliated Hospital of Zhengzhou University, Zhengzhou, China; ²People's Hospital of Zhengzhou, Zhengzhou, China

Received May 10, 2016; Accepted July 19, 2016; Epub December 1, 2016; Published December 15, 2016

Abstract: Objective: This paper aims to analyze the controlling effect on rhythm of the heart by esmolol and landiolol during gastric surgery on elderly patients and to analyze whether they affect anesthesia doses used for surgery, which probably affects postoperative cognitive function. Methods: 45 patients who conducted radical surgery for gastric cancer were collected as study objects and they were randomly divided as group P, group E and group L, and the three groups were respectively given moderate placebo, esmolol and landiolol during the surgery. And then during the surgery, HR (Heart Rate) and MAP (Mean Arterial Pressure) of patients were observed, together with time of opening eyes and extubation time. Bis (Bispectral Index) value was maintained within 40-50. The dose of inhalation Sevoflurane at every moment in the surgery was recorded as well. And finally, their preoperative cognitive level and postoperative cognitive level were evaluated by MMSE (mini-mental state examination). Results: the average eye-open time in group E and group L were 14.3 ± 3.24 min and 15.5 ± 2.26 min, respectively, 4.5 min and 3.3 min ahead of group P, and the average extubation time in group E and group L were 18.8 ± 2.70 min and 19.1 ± 2.33 min, respectively, 7 min and 6.7 min ahead of group P. The average range of HR and MAP of patients in group P, group E and group L were 77.29-91.4 times/min, 70.8-77.8 times/min and 73.4-79.2 times/min, and 79-95.8 mmHg, 70.8-87.8 mmHg and 73.4-88 mmHg, respectively. And early postoperative cognitive function recovery of patients in group E and group L was 2 d and 4 d advanced compared to group P. The dose range of sevoflurane given during the surgery in group P, group E and group L were 2-1.1 MAC, 0.7-0 MAC and 1.4-0.4 MAC. Conclusion: Esmolol and landiolol have certain controlling function over HR and blood pressure during the surgery for the elderly patients, and landiolol is more stable in reducing HR and blood pressure. And at the same degree of anesthesia, esmolol and landiolol can reduce sevoflurane inhalation dose which helps to advance patients' eye-open time and extubation time, consequently to improve their early cognitive function recovery.

Keywords: Esmolol, landiolol, surgery for the elderly patients, anesthesia, cognitive function

Introduction

Esmolol and landiolol both are ultrashort acting β_1 -receptor blocking agent, which are always used to treat arrhythmias during perioperative period [1, 2]. For stimulation during the surgery like anesthesia, tracheal intubation/extubation, and operative procedure, etc., patients will have stresses such as accelerated HR, rising blood pressure and increased myocardial oxygen consumption that will cause abnormalities of cardiovascular function even deaths [3]. There's always a higher risk of arrhythmia among elderly patients in perioperative period than young people. And because excessive anesthesia dose has been given in the surgery causing delayed recovery times [4, 5], the

elderly patients are always likely to have cognitive dysfunction [6]. Besides, hypofunction caused by organs and organization aging, decreasing metabolism of the elderly people will result to weak tolerance for external stimulus, and they usually have several chronic diseases and complications, for example, hypertension, coronary heart disease and diabetes and so on, which both increase the risk for operation. Therefore, medicines used to control rhythm of the heart for the elderly people needs more cautiousness. Though there're many reports on esmolol and landiolol being used to control rhythm of the heart on animals and human side [8-11], there're still few systemic studies on the elderly people's condition-control in the surgery and the effects on their post-

Esmolol and landiolol on elderly patients with gastric surgery

operative cognitive function recovery by esmolol and landiolol.

In this study effects on the elderly patients' rhythm of the heart during gastric surgery and their postoperative cognition were analyzed by using these two β_1 -receptor blocking agents. And the purpose of the study is to analyze the controlling effect on rhythm of the heart by esmolol and landiolol during gastric surgery on elder patients and to analyze whether they affect doses used for surgical anesthesia, consequently to affect postoperative cognitive function.

Materials and methods

Clinical data

Forty-five elderly patients conducted radical surgery for gastric cancer in People's Hospital of Zhengzhou were included in the study. Inclusive standards were as followed: elective surgical patients aging from 60 to 75; American Society of Anesthesiologists (ASA) classification of I-II; patients with no heart disease, hypertension, history of anesthesia and obvious drug-related allergy; Body Mass Index (BMI) < 30; patients with normal language expression, emotion recognition, neural function; patients with oral cavity that could be conducted trachea cannula and without other problems. And they were randomly divided into three groups, placebo group (group P), esmolol group (group E), and landiolol group (group L).

Study methods

All patients were given general anesthesia with tracheal intubation and the specific procedure is as followed: after entering operating room, patients were examined in aspects of MAP, HR and open venous pass; group P, group E and group L were given placebo, esmolol and landiolol, respectively, by intravenous drip at the speed of 125 $\mu\text{g}/\text{Kg}/\text{min}$ for two minutes; and then they were given continuous intravenous drip at the speed of 25~45 $\mu\text{g}/\text{Kg}/\text{min}$; five minutes later they were given anesthesia induction, specifically, 0.2 $\mu\text{g}/\text{Kg}$ of fentanyl, 2 mg/kg of diprivan and 0.3 mg/kg atracurium bolus; after the patients fell asleep, they were given train-of-four stimulation, and when myopalmus was zero, patients were trachea cannula and then were conducted mechanical ventilation; respiratory parameters setting, specifically,

tidal volume: 8~11 ml/kg, breathing rate: 13~15 times/min, end-tidal-carbon dioxide (Et CO_2) tension: 35~45 mmHg; sevoflurane (oxygen flow: 2 L/min) was continuously given during the surgery and then the concentration of inhaling sevoflurane was adjusted to maintain Bis value within 40~50, and the intravenous dripping rate of atracurium is 10 $\mu\text{g}/\text{kg}/\text{min}$; anesthesia was stop after skin closure. When patients recovered consciousness and could breathe spontaneously with swallowing and cough, etc., the tube could be removed. And 10 minutes after tube drawing, the intravenous dripping of placebo, esmolol and landiolol was stop. During the surgery when patients had bradycardia (HR < 40) or MAP < 50 mmHg, the esmolol dose and landiolol dose had been reduced; and when other dangerous consequences happened, responding emergency measures should be taken. And patients' temperature were monitored, insulation measures were taken as well.

Observation indexes

Operation duration, anesthesia maintenance time, eye-open time, extubation time (from time when the anesthesia was stopped to extubation time), time after the start of anesthesia maintenance, when Bis maintained with 40~50, the inhalation dose of sevoflurane was recorded every 10 min (the unit is minimum alveolar concentration (MAC)); patients' HR and MAP were monitored at the following time points: time before being given anesthesia (before being given placebo, esmolol and landiolol) (T1), 5 min after being given the anesthesia (T2), time before being conducted trachea cannula (T3), time being conducted trachea cannula (T4), before skin incision (T5), time being performed skin incision (T6), before abdominal exploration (T7), after abdominal exploration (T8), time the operation was completed (T9), eye-open time (T10), time of extubation (T11), time stop being given the anesthesia (T12) and 30 min after stop being given the anesthesia (T13). And they were performed MMSE scoring by the same doctor at the following times which were 12 h before the operation and 1 h, 6 h, 12 h, 1 d, 3 d, 5 d and 7 d after the operation.

MMSE scoring criteria

Referring to *Rating Scale for Psychiatry* documented by Mingyuan Zhang, patients were con-

Table 1. General situation, postoperative eye-open time and extubation time of patients in the three groups

	Placebo group (n=15)	Esmolol group (n=15)	Landiolol group (n=15)
Gender (male/female)	8/7	8/7	8/7
Chronic disease (volume)	1.07±0.88	1.13±1.06	1.07±1.03
Age	67.6±4.55	67.8±4.62	67.6±4.14
Weight (Kg)	62.9±6.40	63.1±5.74	63.1±7.44
BMI (Kg/m ²)	23.1±1.30	23.2±1.70	23.2±1.73
Operation time (min)	211.3±30.54	209.6±28.02	212.8±31.74
Anesthesia time (min)	271.3±29.61	271.2±24.71	273.8±27.32
Eye-open time (min)	18.8±3.86	14.3±3.24*	15.5±2.26*
Extubation time (min)	25.8±3.38	18.8±2.70*	19.1±2.33*

*Represents that when group E and group L were compared to group P, $P < 0.05$.

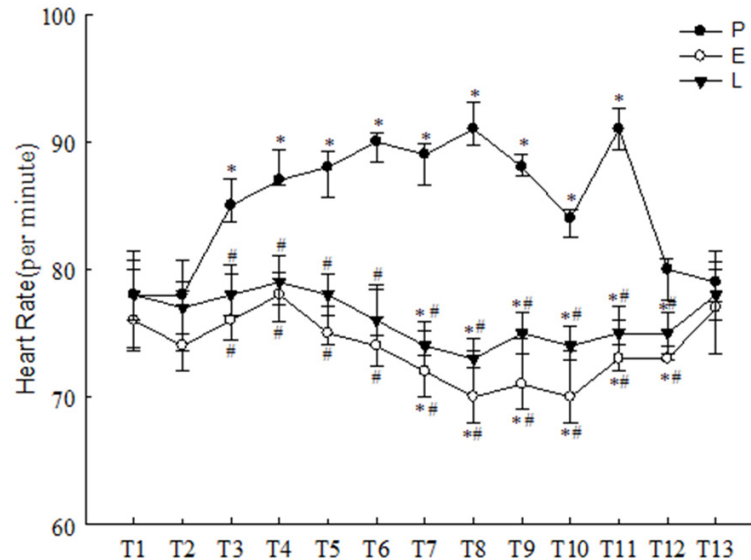


Figure 1. Heart rate (HR) fluctuations regarding perioperative period in the three groups. *Represents comparison between different value at each time point and the basic value, $P < 0.05$; #Means comparison of group E and group L with group P at the same time point, $P < 0.05$.

ducted MMSE scoring according to their education degrees. And the total score of MMSE scoring is 30, and patients will be decided as having impaired cognition function when the MMSE scoring is less than 2 points, the preoperative underlying value [12].

Statistical methods

Data were expressed as mean ± SD; differences in categorical data were evaluated by t test; the primary evaluation was based on comparisons among esmolol group, landiolol group and

placebo group; the differences of perioperative HR, MAP and sevoflurane in three groups were assessed by comparisons within group and among groups. In addition, t test was applied to calculate MMSE score, and SPSS19.0 software was used to deal with data. In this study, $P < 0.05$ indicates statistical significance.

Results analysis

There's no statistical significance among the three groups in terms of weight, BMI, operation time and anesthesia time, etc. ($P > 0.05$). But the eye-open time and extubation time in group E and group L were ahead of that in group P, which indicated that the difference is statistically significant ($P < 0.05$). And differences in group E and group L weren't apparent. The analyzed results are shown in **Table 1**.

HR, MAP and dose of sevoflurane during perioperative period for the three groups were shown as **Figures 1-3**, respectively. And we can see from the figures that the differences of HR and MAP at T1 and T2 among the three groups were not significant ($P > 0.05$), and patients' HR and MAP in group P showed large fluctuations while that in group E and group L were more stable. It can be seen from **Figure 3** that the inhalation doses of sevoflurane of 15 patients at every time point in each group were listed from high to low which in order are group P, group L and group E.

12 h before the operation, the average MMSE of patients in the three groups were 28.1±1.33, 27.9±1.16 and 27.9±1.51, respectively, which had no statistical significance ($P > 0.05$). The MMSE score was listed in **Table 2**. 1 h~1 d after the operation, the MMSE score difference in

Esmolol and landiolol on elderly patients with gastric surgery

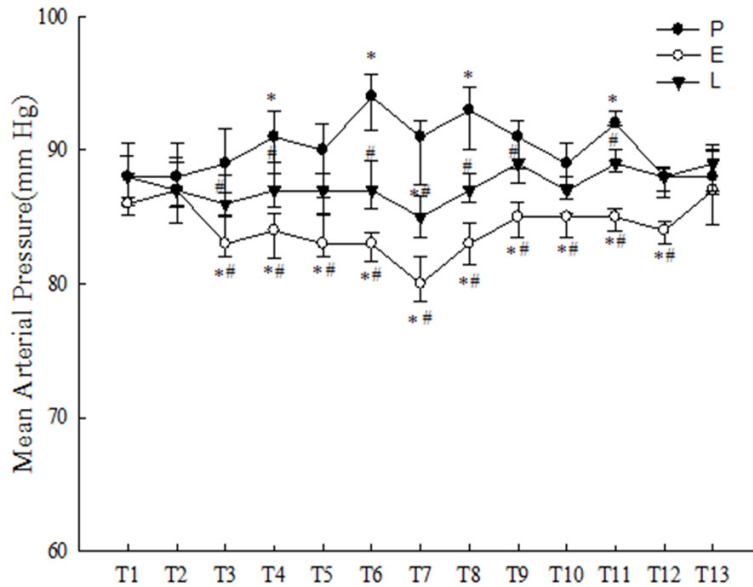


Figure 2. Mean arterial pressure (MAP) fluctuations during perioperative period in the three groups. *Represents comparison between different value at each time point and the basic value, $P < 0.05$; #Means comparison of group E and group L with group P at the same time point, $P < 0.05$.

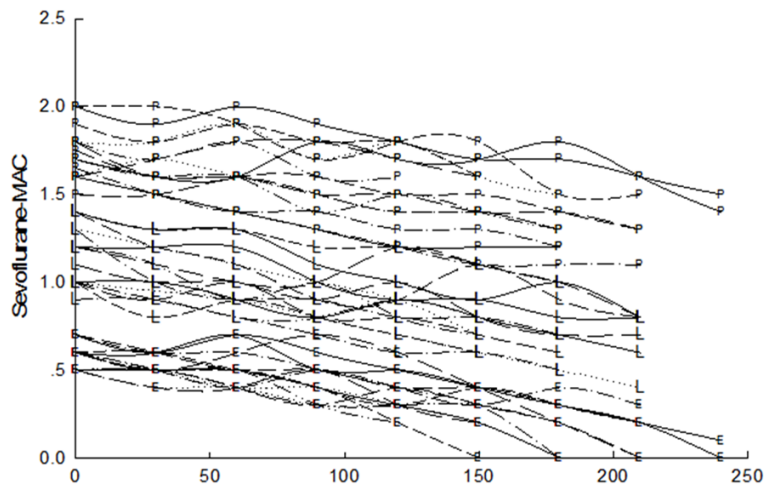


Figure 3. Intraoperative fluctuations of sevoflurane in the three groups. Each patient said in a different line. Inhalation dose of sevoflurane is higher in the placebo group compared to the esmolol and landiolol group, esmolol group is the lowest.

group E and group L had no statistically significance ($P > 0.05$), which is apparently higher than group P.

And the incidence rates of having impaired cognition function a day after the operation in the three groups were 86.7%, 66.7% and 53.3%, respectively; the incidence rates of having impaired cognition function three days after

the operation in the three groups were 53.3%, 26.7% and 40%; the incidence rates of having impaired cognition function 5 days after the operation in the three groups were 53.3%, 13.3% and 20%; and the incidence rates of having impaired cognition function 7 days after the operation in the three groups were 40%, 13.3% and 20%.

Discussion

Due to weak regulating function for vascular sclerosis, the elderly people are sensitive to the change of blood pressure and HR. While esmolol is effective in decreasing blood pressure and HR, thus it's a challenge for elderly patients. But there're reports indicated that esmolol is safe for the elderly people too [13]. And esmolol can not only reduce changes of hemodynamics during the operation but also need less anesthesia amount and advance extubation time [14]. Effect of landiolol and esmolol on fighting arrhythmia is similar but the former is more stable in deceasing HR and it can control blood pressure in the normal rang as well [15]. This study also shows that esmolol and landiolol can control HR during the operation and can reduce dose of sevoflurane used during the operation together with advance patients' eye-open time and extubation time, consequently, patients

can recover cognition level in advance. And landiolol is more stable in controlling patients' rhythm of the heart, which agrees with the studying results of Xiao J, et al. [15].

The eye-open time and extubation time of patients in group E are 14.3 ± 3.24 min, 18.8 ± 2.70 min, which was 4.5 min and 7 min ahead of group P, respectively; the eye-open

Esmolol and landiolol on elderly patients with gastric surgery

Table 2. MMSE scores of patients before and after the operation in the three groups

MMSE score	Placebo group (n=15)	Esmolol group (n=15)	Landiolol group (n=15)
12 h before operation	28.1±1.33	27.9±1.16	27.9±1.51
1 h after operation	9.9±2.02#	16.2±1.32*,#	16.5±1.60*,#
6 h after operation	14.8±1.57#	21.7±2.99*,#	21.5±3.60*,#
12 h after operation	18.5±2.75#	24.7±2.96*,#	24.2±2.88*,#
1 d after operation	23.8±1.61#	25.8±2.62*,#	26.3±1.67*,#
3 d after operation	26.1±1.03#	27.1±1.79	26.9±0.96
5 d after operation	26.5±1.06#	27.5±1.60	27.3±1.18
7 d after operation	26.7±0.90#	27.9±1.75	27.9±1.13

*Represents comparison of group E and group L with group P, $P < 0.05$;

#Indicates comparison among the three groups before and after operation, $P < 0.05$.

time and extubation time of patients in group L are 15.5 ± 2.26 min, 19.1 ± 2.33 min, which was 3.3 min and 6.7 min ahead of group P, respectively. And the average HR and MAP ranges of patients during the operation in the three groups were 77.2~91.4 times/min, 70.8~77.8 times/min and 73.4~79.2 times/min and 79~95.8 mmHg, 70.8~87.8 mmHg and 73.4~88 mmHg, respectively; and we can learn that group P fluctuates dramatically and is significantly higher than the basic value while group E and group L have little fluctuation and were lower than the basic value. It's thus clear that esmolol and landiolol can control patients' HR and blood pressure during the operation, which is in line with the study of Yunfei Wang [16] and Chenlin Hou [17]. Moreover, compared to esmolol, landiolol is more stable in controlling the accelerating HR and increasing blood pressure caused by anesthesia, cannula, extubation and operative procedures during the operation. And esmolol and landiolol are helpful to reduce inhalation dose of sevoflurane thus to decrease cognitive impairment caused by anesthesia. The using dose range of sevoflurane at each time point during the operation for group P, group E and group L are 2~1.1 MAC, 0.7~0 MAC and 1.4~0.4 MAC. The reason why esmolol and landiolol can reduce the inhalation dose of sevoflurane during the operation is that they enhance the antinociceptive effect of nerve centre, consequently to reduce the increasing of Bis value caused by cannula and extubation, etc [18].

The postoperative average MMSE score of patients in group P was significantly lower than

that before the operation, and it recovered to preoperative level on the 5th day after the operation (1.6 points less than that before the operation, and $1.6 < 2$); one hour to one day after the operative, the average MMSE score of group E was apparently lower than that before the operation, and it returned to preoperative level on the third day after the operation (0.8 points less than that before the operation, and $0.8 < 2$); one hour to one day after the surgery, the average MMSE score of group L was dramatically lower than that before the operation, and it returned to

preoperative level on the first day after the operation (1.6 points less than that before the operation, and $1.6 < 2$). Therefore, we can say that landiolol and esmolol are helpful for patients' early postoperative cognition recovery, and group E and group L are two days and four days respectively faster than group P in term of postoperative recovery for cognitive functions. And we inferred that there are two reasons caused differences in cognitive function recovery among the three groups. One is that patients' HR and blood pressure during the operation were controlled by esmolol and landiolol, which reduced the harm done by unstable HR and blood pressure, therefore to help recover patients' early cognitive function; the other is that esmolol and landiolol decreased the dose of inhalation sevoflurane shortening the existence time of sevoflurane in human body and reducing harm to cognitive function done by anesthesia, which in some extent improves patients' recovery of early cognitive function.

Due to limited subject number and single operation type in this study, there's certain limitation for the effect exploration of esmolol and landiolol in the elderly patients during the operation. However, it still has been proved that esmolol and landiolol have positive influences on elderly patients' HR controlling and the dose of anesthesia used in the operation.

Acknowledgements

I wish to thank People's Hospital of Zhengzhou for providing experimental sources for this manuscript.

Disclosure of conflict of interest

None.

Address correspondence to: Shumin Li, People's Hospital of Zhengzhou, No. 33 Huanghe Rd. Jinshui Dist. Zhengzhou, Henan, China. Tel: +861393-7195296; E-mail: Li.shumin@tom.com

References

- [1] Sasao J, Tarver SD, Kindseher JD, Taneyama C, Benson KT and Goto H. In rabbits, landiolol, a new ultra-short-acting β -blocker, exerts a more potent negative chronotropic effect and less effect on blood pressure than esmolol. *Can J Anaesth* 2001; 48: 985-989.
- [2] Wang Hui and Qing Enming. Clinical study on Landiolol Hydrochloride in treatment of tachycardia arrhythmia during operation. *Five-Continental International Conference on Cardiovascular Disease* 2014.
- [3] Lu AP, Dai Y and He BT. Effects of esmolol on stress response patients and hemodynamics of general anesthesia patients. *Mod J Integr Tradit Chin West Med* 2014; 35.
- [4] Türe H, Sayin M, Karlikaya G, Bingol CA, Aykac B and Türe U. The analgesic effect of gabapentin as a prophylactic anticonvulsant drug on postcraniotomy pain: a prospective randomized study. *Anesth Analg* 2009; 109: 1625-1631.
- [5] Bilotta F, Doronzio A, Cuzzone V, Caramia R and Rosa G. Early postoperative cognitive recovery and gas exchange patterns after balanced anesthesia with sevoflurane or desflurane in overweight and obese patients undergoing craniotomies. *J Neurosurg Anesthesiol* 2009; 21: 207-213.
- [6] Chen Y, Wei CW, Yu YJ, Ni XL and Xiong LZ. Relationship between emergence agitation during recovery from general anesthesia and postoperative cognitive dysfunction. *Chin J Anesthesiol* 2013; 33: 34-36.
- [7] Chen MJ and Chu QY. Preliminary discussion on the rational drug use of aged people. *Med Front* 2015.
- [8] Oda Y, Nishikawa K, Hase I and Asada A. The short-acting beta1-adrenoceptor antagonists esmolol and landiolol suppress the bispectral index response to tracheal intubation during sevoflurane anesthesia. *Anesth Analg* 2005; 100: 733-737.
- [9] Saito S, Nishihara F, Akihiro T, Nishikawa K, Obata H, Goto F and Yuki N. Landiolol and esmolol prevent tachycardia without altering cerebral blood flow. *Can J Anaesth* 2005; 52: 1027-1034.
- [10] Goyagi T, Horiguchi T, Nishikawa T, Tobe Y and Masaki Y. Neuroprotective effects of selective β -1 adrenoceptor antagonists, landiolol and esmolol, on transient forebrain ischemia in rats; a dose-response study. *Brain Res* 2012; 1461: 96-101.
- [11] Li M, Sun Z, Zhuang RL, Ma TF, Gu SL, Ma X and Dai TJ. Comparative study of landiolol and esmolol on antiarrhythmic and safety. *Chin J Clin Pharmacol* 2015; 8: 640-644.
- [12] Mon TG, Reno KA, Olsen DC. Postoperative cognition dysfunction is associated with cerebral oxygen desaturations. *Anesthesiology* 2009; 93: 167-185.
- [13] Koutouzis M, Nikolidakis S, Grigoriadis A, Koutsogeorgis D and Kyriakides ZS. Intravenous esmolol is well tolerated in elderly patients with heart failure in the early phase of non-ST elevation myocardial infarction. *Drugs Aging* 2006; 23: 673-680.
- [14] Asouhidou I, Trikoupi A. Esmolol reduces anesthetic requirements thereby facilitating early extubation; a prospective controlled study in patients undergoing intracranial Surgery. *BMC Anesthesiol* 2015; 15: 172.
- [15] Xiao J, He P, Zou Q, Zhao Y, Xue Z, Deng X, Li S, Guo Q, Tao G, Yang T, Lang Z, He J, Wang X. Landiolol in the treatment of the intraoperative supraventricular tachycardia: a multicenter, randomized, double-blind, placebo-controlled study. *J Clin Anesth* 2015; 27: 120-128.
- [16] Wang YF, Qu Y, Meng JH. Analysis on effects of different doses of esmolol on preventing cardiovascular reactions to endotracheal intubation. *World Latest Med Inform* 2015; 32: 104.
- [17] Hou CL, Zhou W, Qing EM, Zhang TZ, Liu GJ, Rong JF, Wu QP, Guo QL, Ai DB and Jin XJ. Evaluation on multicenter efficacy and safety of landiolol on tachycardia arrhythmia during operation. *Chin J Clin Pharmacol Ther* 2015; 20: 1131-1136.
- [18] He GN, Lv HW, Wang JK. Effect of esmolol on the haemodynamics and the bispectral index during induction anesthesia with intravenous propofol/sulfentanil or sevoflurane inhalation. *Chin J New Drugs* 2008; 17: 2141-2143.