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Original contribution

The suppressive effects of landiolol administration on the occurrence of postoperative atrial fibrillation and tachycardia, and plasma IL-6 elevation in patients undergoing esophageal surgery: A randomized controlled clinical trial☆,☆☆

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ABSTRACT

Study objective: To determine whether perioperative landiolol administration suppresses postoperative atrial fibrillation (AF) and the plasma cytokines elevation in patients undergoing esophageal cancer surgery.
Design: A prospective, randomized controlled trial.
Setting: Akita University Hospital, Akita, Japan, from April 2012 to January 2015.
Patients: Forty American Society of Anesthesiologists grade I-II patients undergoing elective esophagectomy.
Interventions: Patients were randomly divided into two groups, landiolol group (landiolol: 5 μg/kg/min) and control group (the same volume of covered saline). Landiolol or saline was infused continuously from the induction of anesthesia until next morning.
Measurements: We examined the new onset of AF and sinus tachycardia, and measured plasma concentrations of cytokines (IL-1β, IL-6, IL-8, IL-10, and TNF-α) just before surgery, at the end of surgery, the next day, and 2 days after surgery. Data (mean ± SD) were analyzed using two-way ANOVA followed by the Bonferroni"s test for post hoc comparison; a $P < 0.05$ was considered statistically significant.
Main results: Demographic data were similar between the landiolol and the control groups. The incidence of AF was significantly lower in the landiolol group (1/19 = 5.3%) compared with the control group (7/20 = 35%) as well as sinus tachycardia (landiolol group, 0/19 = 0% vs. control group, 5/20 = 25%). Plasma IL-6 level at the end of surgery was significantly lower in the landiolol group compared with the control group, but the other plasma cytokines levels were similar between the two groups during the entire study period.
Conclusions: Perioperative landiolol administration suppressed the incidence of new-onset of AF as well as sinus tachycardia, and the plasma IL-6 elevation in patients undergoing esophageal cancer surgery.

1. Introduction

Atrial fibrillation (AF) is the common arrhythmia following the thoracic surgery. The occurrence of postoperative AF is as high as 40% in patients undergoing major non-cardiac thoracic surgery [1–6]. Similarly, the incidence of AF after esophageal resection surgery is reported to be 9–46% [7,8]. The occurrence of postoperative AF has been associated with increased rates of pulmonary and anastomotic complications, resulting in prolongation of hospital stay and increased mortality after esophageal surgery [9–11]. Thus, the prevention of postoperative AF has been a great concern.

According to the 2014 AHA/ACC/HRS Guideline, it is reasonable to manage well-tolerated, new-onset postoperative AF with rate control and anticoagulation with cardioversion if AF does not revert spontaneously to sinus rhythm during follow-up [12]. Pharmacological management is required to control the heart rate and to restore sinus rhythm [13]. Although various prophylactic therapies have been shown to reduce the occurrence of postoperative AF, widespread use has been restricted due to concerns over the potential side effects [1,14–16]. Although β-blockers such as propranolol [17] and metoprolol [18] have been demonstrated to reduce the frequency of postoperative AF in thoracic surgery, the administration of propranolol is associated with an increased risk of hypotension and bradycardia.

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Landiolol hydrochloride (landiolol), an ultra-short-acting, high selective β1-blocker, developed in Japan, and was shown to be beneficial with regards to the reduction of AF and tachycardia during and after surgery without hypotension [19,20]. Moreover, the intraoperative and postoperative administration of low-dose landiolol prevents new-onset AF after cardiac [20–25], pulmonary [26,27] and esophageal [8] surgeries. These studies have concluded that continuous intravenous infusion of landiolol is safe and effective for suppressing AF and tachycardia. However, there are no prospective, randomized controlled studies examining the suppression of AF induced by administration of landiolol in patients undergoing esophageal surgery.

On the other hand, landiolol has been demonstrated to have protective effects in systemic inflammation models, reducing the serum levels of the inflammatory mediators, HMGB-1, and TNF-α as well as histological damage in animal studies [28,29]. We have also reported that landiolol exhibits neuroprotection against transient brain ischaemia [30,31]. These results suggest a protective effect of landiolol against systemic inflammation due to surgery.

The primary outcome of this study was to determine whether low-dose prophylactic landiolol reduces the new-onset of postoperative AF in patients undergoing esophageal cancer surgery. The secondary outcomes included the effects of landiolol on the incidence of sinus tachycardia, on the plasma cytokine changes due to inflammation induced by esophageal cancer surgery, and on the length of hospital stay.

2. Materials and methods

2.1. Patients

Ethical approval for this study (No. 1216) was provided by the Institutional Review Board in Akita University Graduate School of Medicine, Akita, Japan (Chairperson Dr. Hiroshi Abe) on 28 September 2011. The study was registered at UMIN clinical trials registry identifier (UMIN000020238) and conducted from April 2012 to March 2015 in Akita University Hospital. All patients provided written informed consent. We enrolled patients with ASA physical status 1 or 2, who were scheduled to undergo esophagectomy for esophageal cancer. We excluded patients with a history of cardiac (e.g., arrhythmias including AF, conduction abnormalities, antiarrhythmic medications including β-blockers, recent angina pectoris, and myocardial myocardial infarction), pulmonary, or renal disease, and thyroid dysfunction from the study. We randomly divided 40 patients into two groups: the landiolol group and the control group, using a computer generated random numbers table. In the landiolol group, patients received 5 μg/kg/min of landiolol from the induction of anesthesia until the morning on the postoperative day (POD) 1 (around 6 o'clock); patients in the control group received the same volume of covered saline. We blinded the anesthesiologists and surgeons to the study group assignments.

2.2. Anesthesia

The surgeon determined the surgical approach for esophagectomy using the lesion location and preoperative staging. Esophagectomy was performed using video-assisted thoracic surgery in the lateral position, with the patients turned in the supine position depending on the site of anastomosis. Most cases utilized esophageal replacement with gastric conduit, with occasional use of an interposition of the colon. Anastomosis was performed in the cervical or thoracic region, depending on the location of the tumor.

We applied standard patient monitoring including electrocardiogram (ECG), invasive blood pressure, and a pulse oximeter. All patients were anaesthetized by using epidural and general anesthesia technique with propofol and remifentanil, followed by rocuronium administration after the confirmation of epidural catheterization with 1.5% lidocaine (3 ml) administration. $ETCO_2$ was maintained at 34–38 mmHg during anesthesia after tracheal intubation under sevoflurane and remifentanil anesthesia. During the operation, anesthesia was adjusted by increasing and decreasing remifentanil administration to maintain blood pressure and heart rate (±20% change from the baseline value) by the anesthesiologists. Continuous infusion of 0.25% levobupivacaine (4 ml/h) and fentanyl (8 μg/h) was used for postoperative analgesia. After surgery following the discontinuation of sevoflurane and remifentanil, patients were allowed to awaken, and the trachea was extubated under sedation by dexmedetomidine administration (0.5 μg/kg/h), which was continued until next morning. We then moved patients into the intensive care unit (ICU).

2.3. Measurements

We recorded the ECG during anesthesia and the ICU stay to identify arrhythmia. If we detected AF or sinus tachycardia (100 > bpm) for 10 min during the study period, we deemed this arrhythmia positive. Also, we recorded blood pressure and heart rate before anesthesia, after arrival at the ICU, and at 8 o'clock in the morning on POD1 and POD2. We collected blood samples after the induction of anesthesia, after the surgery, on the POD1, and on the POD2 to measure plasma cytokines concentrations. The supernatant fluid was collected and stored at −20 °C until analysis after centrifuging the blood samples for 15 min at 3000 rpm. The measurement of plasma cytokines included interleukin (IL)-1β, IL-6, IL-8, IL-10, and tumor necrosis factor (TNF)-α; we measured plasma cytokines concentrations using a specialized laboratory (SRL, Inc. Tokyo, Japan).

2.4. Statistical analyses

We calculated a sample size to assess an effect size of 0.9 on the basis of a preliminary study and previous studies [32,33]. Using the G*Power, the required sample size was 32 patients with an alpha error of 0.05 and 80% power [34]. As we considered losses to follow-up (drop outs), we enrolled 40 patients in our study.

We expressed values as mean ± SD and numbers. The detection thresholds were 10 pg/ml for IL-1β, and 2 pg/ml for IL-8 and IL-10. Therefore, if the values were under the detection threshold, the values were regarded as 10 pg/ml for IL-1β, and 2 pg/ml for IL-8 and IL-10, respectively. Student's *t*-test was used to compare the demographic data. The cytokine concentrations at each time in the both groups were analyzed using two-way ANOVA followed by the Bonferroni's test for post hoc comparison. Categorical data (incidence of arrhythmia) were compared using the Chi-square test, with a significance level of $P < 0.05$. We performed analysis using GraphPad Prism 6 (GraphPad Software, Inc., San Diego, U.S.A.)

Table 1
Patient demographics and surgical data.

	Control group $n = 20$	Landiolol group $n = 19$	*P* value
Height (cm)	163.9 ± 6.2	160.4 ± 7.2	0.10
Weight (kg)	56 ± 11.2	54.7 ± 7.7	0.66
Age (years)	63 ± 8	67 ± 7	0.08
Gender (male/female)	18 / 2	15 / 4	0.41
No. of patients with HT	8	6	0.51
No. of patients with DM	1	2	0.61
Time of surgery (min)	535 ± 90	538 ± 88	0.91
Time of anesthesia (min)	645 ± 98	637 ± 90	0.72
Hb before surgery (g/dl)	12.0 ± 1.6	12.0 ± 1.4	0.92
Rivised Cardiac Risk Index	1.05 ± 0.2	1.10 ± 0.3	0.50
Time of landiolol infusion (hour)	0	20.5 ± 7.5	–

Values are mean ± SD or numbers. HT = hypertesion, DM = diabetes mellitus. Hb = hemoglobin concentration.