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CLINICAL REPORT

Low-dose continuous infusion of landiolol can reduce adrenergic response during tracheal intubation in elderly patients with cardiovascular disease

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Abstract The objective of this study was to examine the effects of low-dose infusion of landiolol on hemodynamics during tracheal intubation in elderly patients with cardiovascular disease. The study population consisted of 30 patients with American Society of Anesthesiologists physical status II and III, aged 65–77 years, who were scheduled to undergo elective surgery under general anesthesia. Patients were randomly divided into two groups ($n = 15$ each): a control group, receiving normal saline, and a landiolol group, receiving landiolol at 30 μg/kg/min. After oxygenation, 1 μg/kg of fentanyl was injected intravenously, followed by continuous infusion of normal saline or landiolol for 5 min. General anesthesia was induced and maintained with target-controlled infusion of propofol at a blood concentration of 4 μg/ml and tracheal intubation was performed 3 min after vecuronium injection. Heart rate, blood pressure, and bispectral index were measured before and after tracheal intubation. Results showed that low-dose continuous infusion of landiolol is an effective and relatively safe method of preventing an intubation-induced adrenergic response in elderly patients with cardiovascular disease.

Keywords Landiolol · Elderly patients · Adrenergic response

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Introduction

Tracheal intubation stimulates adrenergic responses, leading to tachycardia and hypertension. Tachycardia is one of the major risk factors for intraoperative myocardial ischemia because of the imbalance in oxygen demand versus supply in the myocardium. In particular, elderly patients are at a high risk for coronary disease [1, 2], so the prevention of perioperative tachycardia in these patients is desirable.

Many prospective studies have reported that landiolol can prevent adrenergic responses during tracheal intubation or extubation [3–7]. However, most previous studies have focused on low-risk patients who are relatively young and have no cardiovascular disease.

The goals of the current study were to determine whether the administration of low-dose continuous infusion of landiolol is safe and whether it attenuates the adrenergic response during tracheal intubation in elderly patients with cardiovascular disease.

Case report

The Institutional Ethics Committee at Sapporo Medical University (Sapporo, Japan) approved this study, and all patients provided their written informed consent. Subjects comprised 30 patients (age range 65–77 years) who had been diagnosed with hypertension and/or ischemic heart disease (American Society of Anesthesiologists physical status class II and III) and were scheduled to undergo elective surgery under general anesthesia. Patients with a history of bronchial asthma, recent myocardial infarction, cerebrovascular disease, or active liver disease were excluded from the study. Patients taking beta-blockers as an antihypertensive medication were also excluded.

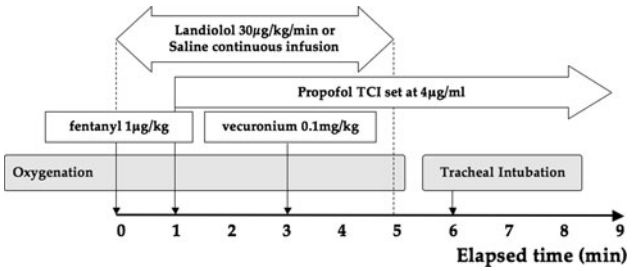

Fig. 1 Study protocol. *TCI* target-controlled infusion

The 30 patients were divided into two groups ($n = 15$ each): a control group, which received normal saline, and a landiolol group, which received landiolol at 30 μg/kg/min.

Upon arrival in the operating room, noninvasive blood pressure (BP), heart rate (HR), arterial oxygen saturation and bispectral (BIS) index were monitored.

Figure 1 shows the protocol for this study. After oxygenation, patients received an intravenous (iv) bolus of fentanyl at 1 μg/kg, followed by the continuous administration of normal saline (control group) or landiolol at 30 μg/kg/min (landiolol group) for 5 min. One minute after the administration of fentanyl, general anesthesia was induced and maintained using propofol with a target-controlled infusion device (TE-371; Terumo, Tokyo, Japan) set at 4 μg/mL until the end of the study. Two minutes after propofol administration and loss of consciousness, patients received manual ventilation with 100% oxygen and vecuronium (0.1 mg/kg). Tracheal intubation was performed 3 min after the administration of vecuronium. BP, HR, and BIS index were recorded every minute until the end of study.

Data are expressed as mean ± standard deviation. Differences between groups were examined for statistical significance using an unpaired *t* test. Continuous variables were analyzed using analysis of variance followed by the Scheffè post hoc test, and a chi-square test was used for analysis of categorical variables. *P* values of less than 0.05 were considered statistically significant.

The two study groups were comparable with respect to age, gender, weight, and height (Table 1).

Figure 2 shows changes in SBP and HR during the study. Baseline values of SBP and HR were similar. No significant differences in SBP or HR were observed between the two groups before intubation. In the control group only, tracheal intubation resulted in a significant increase in SBP and HR compared with baseline.

Administration of propofol significantly decreased the BIS index in both groups before intubation (47 ± 7 and 45 ± 5 in the control and landiolol groups, respectively), and tracheal intubation slightly increased the BIS index (49 ± 9 and 47 ± 9 in control and landiolol groups, respectively). There were no significant differences in the BIS index between the groups.

Table 1 Demographic data for the control and landiolol groups in this study

	Control group ($n = 15$)	Landiolol group ($n = 15$)
Age (years)	69 ± 5	71 ± 5
Gender (F/M)	9/6	10/5
Height (cm)	158 ± 7	159 ± 9
Weight (kg)	54 ± 8	57 ± 10
Complications		
Hypertension	13	12
Ischemic heart disease	2	3
Diabetes mellitus	3	4
ASA physical status		
II	14	13
III	1	2

The two study groups were comparable with respect to age, gender, weight and height as well as ASA physical status

ASA American Society of Anesthesiologists

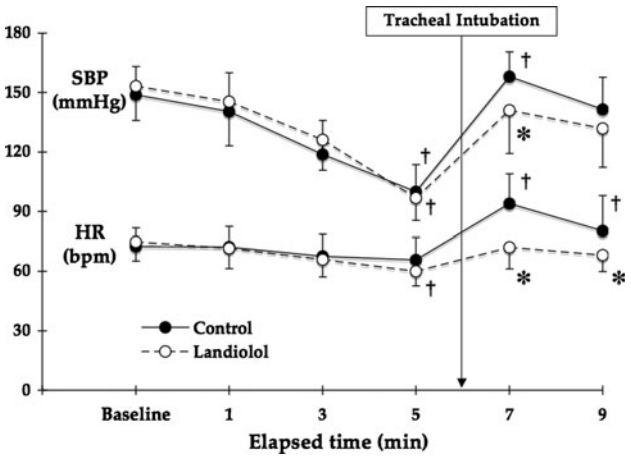

Fig. 2 Changes in systolic blood pressure (*SBP*) and heart rate (*HR*) during the study protocol. Data are expressed as mean ± standard deviation. Group consists of a control group ($n = 15$) and a landiolol group ($n = 15$). $^{\dagger}P < 0.05$ versus the baseline value in each group, $^{*}P < 0.05$ versus the control group at each elapsed time

Discussion

Results show that low-dose landiolol can attenuate hypertension and/or tachycardia caused by tracheal intubation without hemodynamic instability and changes in anesthetic depth.

Although many studies have shown the efficacy of the prophylactic administration of landiolol [3–7], no previous reports have focused on elderly patients with cardiovascular disease, who are at high risk for perioperative myocardial infarction, as individuals who would benefit from anti-adrenergic therapy.

In general, the recommended dose of landiolol is 125 μg/kg/min for 1 min followed by 40–60 μg/kg/min

[3, 4]. This "high dose" was based on the results of a clinical trial of individuals (average age 45 ± 12 years) at low risk of cardiovascular events [4]. While the recommendations indicate that the dose of landiolol should be reduced in high-risk patients such as elderly patients with cardiovascular disease, the effective and safe dosage of landiolol for high-risk patients remains unclear.

Therefore, we conducted a preliminary study of the effects of three low doses of landiolol, 15, 30 and 60 μg/kg/min ($n = 5$ for each group), on the adrenergic response to tracheal intubation. In the 60 μg/kg/min group, three patients (60%) had bradycardia (HR < 45 bpm) and four patients (80%) had hypotension (BP < 75 mmHg) before tracheal intubation, while at 15 μg/kg/min there was little effect on the adrenergic response to tracheal intubation. Therefore, the present study investigated only the 30 μg/kg/min group.

Interestingly, Sugiura et al. [5] and Kadoi et al. [7] reported that landiolol could be less effective in hypertensive patients compared to normotensive patients. These results might be caused by the differential adrenoreceptor sensitivity between hypertensive and normotensive patients. Based on these studies, in elderly patients without hypertension, the required dose of landiolol for attenuating adrenergic response may be less than that needed for hypertensive patients, such as our demographics. In addition, we used fentanyl as an analgesic agent. If remifentanil is applied, the dose of landiolol or remifentanil should be reduced because remifentanil has more of a suppressive effect on hemodynamics than fentanyl [8].

We also investigated whether low-dose landiolol attenuates the BIS index before and after intubation. Several studies have reported that landiolol can suppress the BIS index [9] or that the dose of propofol required to induce anesthesia is decreased by landiolol [10]. The present study found no significant differences in the BIS index between the control and landiolol groups, suggesting that low-dose landiolol has little additional anesthetic effect. The anesthetic effect of landiolol requires further investigation, because the reduction in the dose required to induce anesthesia caused by landiolol may simply represent an outcome of negative inotropic effects.

In conclusion, low-dose continuous infusion of landiolol can reduce tachycardia and hypertension caused by tracheal intubation without hemodynamic deterioration in elderly patients with cardiovascular complications.

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