Journal of Clinical Anesthesia (2015) **27**, 120–128

ELSEVIER

Journal of Clinical Anesthesia

Original Contribution

Landiolol in the treatment of the intraoperative supraventricular tachycardia: a multicenter, randomized, double-blind, placebo-controlled study☆

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Received 29 August 2013; revised 17 July 2014; accepted 18 July 2014

Keywords:
Landiolol;
Esmolol;
Intraoperative supraventricular tachycardia;
Efficacy;
Safety

Abstract

Background: Supraventricular tachycardia during the induction of anesthesia may carry a higher risk.
Study objective: The aim of this study was to evaluate efficacy and safety of intravenous landiolol in Chinese patients with intraoperative supraventricular tachycardia during anesthesia.
Design: A randomized, double-blind, placebo-controlled, parallel-group, multicenter, phase 2 study.
Setting: Eight sites of Chinese hospitals.
Patients: Men and women aged 18 to 70 years with the intraoperative supraventricular tachycardia

☆ Authors' contribution: J Xiao and XR Wang contributed to the conception and design of the research and assisted in protocol development; J Xiao was involved in the drafting the article or revising it critically for important intellectual content. All authors were involved in the acquisition of data or analysis and interpretation of data. All authors critically reviewed and approved the submission. The authors had complete access to the data that support the publication.

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http://dx.doi.org/10.1016/j.jclinane.2014.07.003

(heart rate [HR], ≥100 beats/min) or the supraventricular tachycardia outside of the sinus tachycardia lasting more than 1 minute.
Interventions: Patients received landiolol or placebo—0.125 mg kg^{-1} min^{-1} (1 minute) loading→0.04 mg kg^{-1} min^{-1} (10 minutes) continuous.
Measurements: The proportion of patients receiving rescue medication (esmolol) when the reduction of HR did not exceed 10% after intravenous landiolol for 5 minutes. Other secondary efficacy end points include HR, blood pressure, rate pressure product, and electrocardiogram; the improvement of supraventricular tachycardia; the time it takes for the decrease of the HR to reach more than 10%; and the time it takes for the HR to reach <100 beats/min.
Main results: Efficacy and safety were evaluated for 240 patients who received study drug. Lower proportions of patients received rescue medication in the landiolol group (7.63%) compared with that in the placebo group (80.33%) ($P < .0001$). Suppression of HR and rate pressure product was generally more potent ($P < .0001$), and higher proportions of patients improved supraventricular tachycardia ($P < .0001$) in the landiolol group. The most frequent adverse event was hypotension.
Conclusion: Intravenous landiolol (loading dose of 0.125 mg/kg) may effectively control intraoperative supraventricular tachycardia during anesthesia. It inhibited the increases in HR during the induction of anesthesia. The effect of landiolol on blood pressure was minimal without decreasing diastolic blood pressure and with the minor reduction of systolic blood pressure (ClinicalTrials.gov number, ChiCTR-TRC-12003021).

1. Introduction

Adverse cardiovascular changes such as supraventricular tachycardia often occur during anesthesia. Supraventricular tachycardia may carry a higher risk in terms of myocardial ischemia [1]. Managing intraoperative supraventricular tachycardia becomes an important goal in the anesthetic management of patients. β-Blockers play an important role in preventing the perioperative myocardial ischemia in patients with coronary artery disease [2].

Landiolol is a selective β1-blocker that was approved in the postoperative use, but it was limited to intraoperative use in Japan in 2006 [3]. Pharmacologic characteristics of landiolol include more potent β1-blocking activity, more cardioselectivity, less effect on blood pressure (BP) and shorter half-life than esmolol [4,5]. Unlike esmolol with hypotensive effects [6], landiolol has little effect on BP in humans [7] and may be used safely in intraoperative setting. The dose-dependent cardiovascular actions of intravenous bolus administration of landiolol in treating tachycardia during the anesthetic management of patients undergoing noncardiac general surgery have been studied and reported [8]. However, the safety and efficacy of landiolol in the intraoperative setting have not been fully evaluated. Therefore, this clinical study was conducted to evaluate and confirm the efficacy and tolerability of landiolol in patients with intraoperative supraventricular tachycardia during anesthesia.

In phase 1, placebo-controlled trials, pharmacokinetics and pharmacodynamics of landiolol in healthy volunteers were determined. The rapid onset and short action of landiolol are expected to offer benefits in acute treatment of patients with unstable hemodynamic conditions [9]. In our phase 2, placebo-controlled trial, we aimed to determine the efficacy and safety of landiolol: 0.125 mg kg^{-1} min^{-1} (1 minute) loading→0.04 mg kg^{-1} min^{-1} (10 minutes) continuous in Chinese patients with intraoperative supraventricular tachycardia during anesthesia.

2. Materials and methods

2.1. Study design

This randomized, double-blind, placebo-controlled, parallel-group, multicenter, phase 2 study was conducted at 8 sites of China from September 2010 to June 2012. The study consisted of a 1-week drug-free screening/run-in phase. The purpose of the screening/run-in phase (visit 1) was to confirm patient's eligibility for the study. Heart rate (HR), BP, and electrocardiography (ECG) were measured before administration (visit 2). Anesthesia was induced with midazolam (0.03-0.04 mg/kg), propofol (1.5-2.0 mg/kg), fentanyl (2.0-3.0 μg/kg), and rocuronium (0.6 mg/kg) and maintained with sevoflurane (1 MAC) and intravenous propofol (4.0-10 mg kg^{-1} h^{-1}) and rocuronium (0.3-0.6 mg kg^{-1} h^{-1}). Patients were ventilated (IPPV Intermittent Positive Pressure Ventilation) with a tidal volume of 7 to 8 mL/kg and 8 to 14 per minute. The ECG and BP were monitored continuously.

The study begun 30 minutes after the start of surgery. At this time, if HR exceeded 100 beats/min, the sinus tachycardia lasted more than 3 minutes, or the supraventricular tachycardia outside of the sinus tachycardia lasted more than 1 minute, except for tachycardia resulting from specific causes such as hypovolemia, light anesthesia, the patients were included in the study. Patients were randomized into 2 groups: the experimental group receiving an intravenous landiolol (0.125 mg kg^{-1} min^{-1}) for 1 minute and those