Safety and efficacy of landiolol hydrochloride for prevention of atrial fibrillation after cardiac surgery in patients with left ventricular dysfunction: Prevention of Atrial Fibrillation After Cardiac Surgery With Landiolol Hydrochloride for Left Ventricular Dysfunction (PLATON) trial

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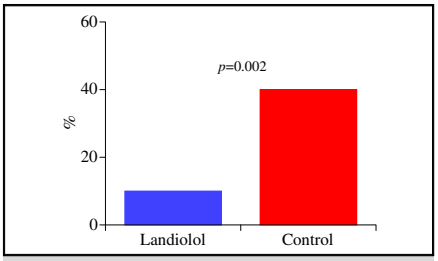
ABSTRACT

Objectives: We previously conducted a prospective study of landiolol hydrochloride (INN landiolol), an ultrashort-acting β-blocker, and reported that it could prevent atrial fibrillation after cardiac surgery. This trial was performed to investigate the safety and efficacy of landiolol hydrochloride in patients with left ventricular dysfunction undergoing cardiac surgery.

Methods: Sixty patients with a preoperative left ventricular ejection fraction of less than 35% were randomly assigned to 2 groups before cardiac surgery and then received intravenous infusion with landiolol hydrochloride (landiolol group) or without landiolol (control group). The primary end point was occurrence of atrial fibrillation as much as 1 week postoperatively. The secondary end points were blood pressure, heart rate, intensive care unit and hospital stays, ventilation time, ejection fraction, biomarkers of ischemia, and brain natriuretic peptide.

Results: Atrial fibrillation occurred in 3 patients (10%) in the landiolol group versus 12 (40%) in the control group, and its frequency was significantly lower in the landiolol group ($P = .002$). During the early postoperative period, levels of brain natriuretic peptide and ischemic biomarkers were significantly lower in the landiolol group than the control group. The landiolol group also had a significantly shorter hospital stay ($P = .019$). Intravenous infusion was not discontinued for hypotension or bradycardia in either group.

Conclusions: Low-dose infusion of landiolol hydrochloride prevented atrial fibrillation after cardiac surgery in patients with cardiac dysfunction and was safe, with no effect on blood pressure. This intravenous β-blocker seems useful for perioperative management of cardiac surgical patients with left ventricular dysfunction. (J Thorac Cardiovasc Surg 2015;150:957-64)



Postoperative atrial fibrillation was significantly lower in the landiolol group.

Central Message

Landiolol hydrochloride seems to be useful for perioperative management of cardiac surgical patients with left ventricular dysfunction.

Perspective

Low-dose infusion of landiolol hydrochloride prevented atrial fibrillation after cardiac surgery in patients with cardiac dysfunction and was safe, with no effect on their blood pressure.

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A number of large-scale studies have demonstrated that β-blockers improve the survival of patients with cardiac failure and myocardial infarction as a result of their sympathoinhibitory and cardioprotective effects.[1,2] Most of the previous studies have investigated oral β-blockers, however, and data on injectable β-blockers are inadequate. In addition, none of the studies of β-blockers were actually conducted in patients undergoing cardiac surgery. The role of β-blockers is currently attracting attention because cardiac surgery provokes a pathologic state of neurohumoral

Abbreviations and Acronyms

POAF = postoperative atrial fibrillation
ACCF = American College of Cardiology Foundation
AHA = American Heart Association
HR = heart rate
PLATON = Prevention of Atrial Fibrillation After Cardiac Surgery With Landiolol Hydrochloride for Left Ventricular Dysfunction [trial]
ICU = intensive care unit
hs-CRP = high-sensitivity C-reactive protein
BNP = brain natriuretic peptide

hyperactivity, including sympathetic overactivity. It is particularly important to prevent atrial fibrillation after cardiac surgery, because atrial fibrillation not only influences cardiac events and cerebral complications in the early postoperative period but also affects the long-term prognosis. Postoperative atrial fibrillation (POAF) is a common complication of cardiac surgery, and its incidence has been variously reported as 16% to 85%.[3-7] POAF often occurs in the early period after surgery and has an influence on stroke and early postoperative cardiac events, as well as on the long-term prognosis,[8] so prevention is important.

For the prevention of POAF, amiodarone and oral β-blockers are recommended in the American College of Cardiology Foundation (ACCF) and American Heart Association (AHA) guidelines.[9] Although the prophylactic administration of oral β-blockers is recommended, there have been few prospective studies on injectable β-blockers, and their efficacy has not been demonstrated, probably because the injectable drugs are more likely to cause hypotension or cardiac failure through their negative inotropic effect.[10,11]

Landiolol hydrochloride (INN landiolol) was developed in Japan. Landiolol shows high β_1 selectivity, with its cardioselectivity (β_1/β_2-receptor activation) being reported to be 8 times that of esmolol and 375 times that of propranolol. In addition, it has an extremely short half-life of approximately 4 minutes. When landiolol and esmolol were compared, both drugs caused a dose-dependent decrease of heart rate (HR), and esmolol also caused a marked decrease of blood pressure, whereas landiolol showed less effect on blood pressure because it has a weaker negative inotropic effect and a stronger chronotropic effect than esmolol.[12-15]

Because of these characteristics, we considered that landiolol was the most appropriate injectable β-blocker for patients with unstable postoperative hemodynamics, and we have previously conducted 2 prospective studies (the Prevention of Atrial Fibrillation in Patients Having Cardiac Surgery with Landiolol Hydrochloride for Coronary Artery Bypass Grafting (PASCAL) and Effect of Beta-Blockers for Prophylaxis of Atrial Fibrillation after Coronary Artery Bypass Grafting with Intravenous Landiolol Hydrochloride and Oral Bisoprolol Administration (BABYLON) trials) on the use of landiolol during cardiac surgery. Both studies provided evidence that landiolol prevents POAF, presumably because it has anti-ischemic, anti-inflammatory, and antioxidant effects in addition to the standard actions of a β-blocker.[16,17] A prospective study has not been performed to assess the safety and efficacy of landiolol for preventing POAF in patients with left ventricular dysfunction, however, so we conducted this clinical trial to determine the safety and efficacy of landiolol for prevention of POAF in patients with left ventricular dysfunction undergoing cardiac surgery (Prevention of Atrial Fibrillation After Cardiac Surgery With Landiolol Hydrochloride for Left Ventricular Dysfunction [PLATON] trial.

MATERIALS AND METHODS

Study Protocol

The PLATON trial was a randomized, open-label study. It was conducted after obtaining approval from the ethics committee of Nihon University School of Medicine Itabashi Hospital. Informed consent was provided by each patient after they received an explanation about this study. This study was registered with the University Hospital Medical Information Network (study ID: UMIN000002160).

The subjects were patients who underwent cardiac surgery under cardiopulmonary bypass and had left ventricular dysfunction (left ventricular ejection fraction $\leq$35% on preoperative left ventricular angiography or echocardiography before surgery). We excluded patients with sinus bradycardia (resting HR $\leq$50 beats/min), second- or third-degree atrioventricular block, clinical hypothyroidism or hyperthyroidism, history of arrhythmia, surgery with circulatory arrest or left ventriculotomy, and planned off-pump surgery. Because the target population of this study, cardiac surgical patients with left ventricular dysfunction, is relatively small, we estimated that the feasible number of patients for recruitment was 30 per group. In our 2 previous studies, the incidences of POAF were approximately 35% in the placebo group and approximately 10% in the landiolol group.[16,17] The incidence of POAF was therefore estimated to be 35% in the control group, and it was assumed that it would be decreased to 10% by treatment with landiolol. With 30 patients per group and the level of significance set at 5%, the power of detection was calculated to be 78%, suggesting that a sample size of 60 was sufficient for this study.

The patients were randomly assigned to 2 groups (a landiolol group and a control group of patients who did not receive landiolol) by the lottery method before surgery. We asked medical staff who were not involved in the surgery or postoperative management to choose an envelope containing the group assignment (landiolol group or control group) when the patient entered the operating room. Physicians and nurses involved in the surgery or postoperative management were not blinded, but the patients were blinded to the treatment assigned, as were the researchers who compiled the results.

In the landiolol group, infusion of landiolol hydrochloride (Ono Pharmaceutical Co, Ltd, Osaka, Japan) was started at a rate of 2 μg/kg/min at the time of weaning from cardiopulmonary bypass and

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