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Clinical role and efficacy of landiolol in the intensive care unit

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Abstract
Beta-adrenergic receptor blockers have proved to be effective for the management of various cardiovascular diseases and the prevention of perioperative cardiac events and cerebrovascular accidents. Landiolol is a short-acting beta-blocker, with high beta 1-selectivity and a short duration of action. We thought landiolol was valuable and suitable for intensive care unit (ICU) patients, and conducted a retrospective study. The records of 80 patients (58 post-surgical patients; group S and 22 internal medicine patients; group IM) were reviewed. Thirty-seven (64%) of the group S patients were post-coronary artery bypass graft surgery, and the IM group consisted mostly of patients with acute myocardial infarction. The most common indication for landiolol in group S was the prevention of myocardial ischemia (50%), and in group IM, it was atrial fibrillation (45%). The median infusion rate of landiolol was 5 μg·kg^{-1}·min^{-1} and the median infusion time was 2 days. Twenty-six patients were continued on oral beta-adrenergic receptor blockers. Landiolol reduced heart rate significantly without reducing blood pressure, and stabilized hemodynamics. We confirmed that landiolol is valuable as a bridge to starting oral beta-adrenergic receptor blockers and as an anti-arrhythmic agent, and that it is suitable for ICU patients due to its high beta 1-selectivity and rapid onset and offset of action.

Key words Landiolol · Beta-adrenergic receptor blocker · Intensive care unit · Atrial fibrillation · Myocardial ischemia

Introduction

Beta-adrenergic receptor blockers have proven to be effective for the management of various cardiovascular diseases, such as ischemic heart disease [1–3], tachycardiac arrhythmias [4–9], hypertension [10,11], and chronic heart disease [12,13], and for the prevention of perioperative cardiac events and cerebrovascular accidents [2,14,15].

There are two short-acting beta 1-selective beta-adrenergic receptor blockers, landiolol and esmolol. Landiolol (ONOACT; Ono Pharmaceutical, Osaka, Japan) is an ultra-shortacting beta-adrenergic receptor blocker that has a higher beta 1-selectivity ($beta_1/beta_2$ = 255) and a shorter elimination $t_{1/2}$ (4 min in healthy subjects) than any of the other currently available beta-adrenergic receptor blockers [16,17].

We though that landiolol would be valuable as a bridge to starting oral beta-adrenergic receptor blockers and that it would be suitable for intensive care unit (ICU) patients, due to its high beta 1-selectivity and rapid onset and offset of action. We conducted a retrospective study to investigate its clinical use and efficacy in the intensive and coronary care unit.

Patients and methods

We conducted a retrospective review of the medical records of intensive and coronary care unit patients at the Nippon Medical School Hospital from April 2004 to June 2005. Landiolol was administered to 80 patients during this time period. The records of all 80 patients were reviewed and the following data were collected: age, sex, reason for ICU admission, indication for landiolol, infusion rate, infusion time, blood pressure (BP) and heart rate (HR) before and soon after stopping landiolol, catecholamine use, and transition to oral beta-adrenergic receptor blockers.

The indications for landiolol administration in our ICU were: tachycardia (HR ≥ 100 beats per min) resulting in unstable hemodynamics, postoperative atrial fibrillation (Af; HR ≥ 80 beats per min), or coronary artery bypass graft (CABG) surgery. Landiolol was

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administered from the start of CABG operations to prevent myocardial ischemia. Bradycardia (HR ≤ 50 beats per min) was a contraindication for landiolol administration. The initial infusion rate was 5–10 μg·kg^{-1}·min^{-1}, titrated in increments of 1–2 μg·kg^{-1}·min^{-1}.

This study conformed to the rules of the Nippon Medical School ethics committee. Data were analyzed using the Wilcoxon signed-rank test and the Greenhouse-Geisser epsilon. The statistics were calculated using SPSS II (Abacus Concepts, Berkeley, CA, USA). Values for results were presented as means ± SD and medians (rate of infusion, duration of infusion), and a P value of less than 0.05 was considered statistically significant.

Results

The patients' characteristics are outlined in Table 1. The records of 80 patients (66 men and 14 women) were reviewed. The reasons for ICU admission are shown in Table 2 and Table 3. There were 58 post-surgical patients (group S) and 22 internal medicine patients (group IM). Sixty-four percent of the group S patients were post-CABG surgery, and the IM group consisted mostly of patients with acute myocardial infarction (AMI). Of the AMI patients, 4 were in cardiogenic shock before landiolol administration. There was no further hemodynamic deterioration in these patients after landiolol administration.

Table 1. Patient characteristics

Sex (male/female)	66/14
Age (years)	67.2 ± 13.0
S/IM	58/22

S, post-surgical patients; IM, internal medicine patients

Table 2. Reasons for ICU admission (post-surgical patients)

CABG	34
CABG, MVP	2
CABG, AVR	1
MVP	2
AVR	1
DVR	1
TAA and AAA	6
Esophagectomy	3
Gastrectomy	2
Duodenal ulcer	2
PD	2
Sigmoidectomy	1
Pheochromocytoma	1

CABG, coronary artery bypass graft surgery; MVP, mitral valve plasty; AVR, aortic valve replacement; DVR, double valve replacement; TAA, thoracic aortic aneurysm; AAA, abdominal aortic aneurysm; PD, pancreaticoduodenectomy

Landiolol reduced HR significantly, from 105.5 ± 22.8 to 83.8 ± 8.3 beats per min ($P < 0.001$) without reducing BP (Fig. 1). The most common indication for landiolol in group S was the prevention of myocardial ischemia (50%), and in group IM it was Af (45%; Figs. 2 and 3). In patients where landiolol was used for the prevention of myocardial ischemia, it was administered from the start of the operation, to control HR and prevent postoperative tachycardia. Of the 27 patients with Af (17 in group S and 10 in group IM), 13 (48%) converted to sinus rhythm (8 in group S and 5 in group IM), and HR was reduced in 8 (30%; 6 in group S and 2 in group IM; Fig. 4). Catecholamine use did not significantly influence HR ($P = 0.094$; Fig. 5); also see Table 4.

No loading doses were given, and the median infusion rate was 5 μg·kg^{-1}·min^{-1}. The median infusion time was 2 days. Twenty-six patients (33%) were continued on oral beta-adrenergic receptor blockers: 24 on carvedilol, 1 on metoprolol, and 1 on sotalol.

Seven patients (9%) died in the ICU: 3 from sepsis, 2 from cardiogenic shock due to AMI, 1 from hemorrhagic shock, and 1 from acute respiratory distress syndrome. The AMI patients were in cardiogenic shock before the landiolol administration, and there was no further hemodynamic deterioration after the landiolol administration. There were no adverse effects such as severe left ventricular dysfunction, severe hypotension, severe bradycardia, bronchospasm, deterioration of diabetes mellitus, or peripheral vascular disease.

Discussion

This is the first report investigating the clinical use of landiolol in the ICU. In this study, landiolol reduced HR significantly without reducing BP and it stabilized hemodynamics. We were able to use landiolol safely in ICU

Table 3. Reasons for ICU admission (internal medicine patients)

AMI	10
Cardiac tamponade	2
UA	1
DCM	1
CHF	1
TAA	1
Long QT syndrome	1
Acute pulmonary edema	1
ARDS	1
Behçet's disease	1
Acute pancreatitis	1
Ulcerative colitis	1

AMI, acute myocardial infarction; UA, unstable angina; DCM, dilated cardiomyopathy; CHF, congestive heart failure; TAA, thoracic aortic aneurysm; ARDS, acute respiratory distress syndrome

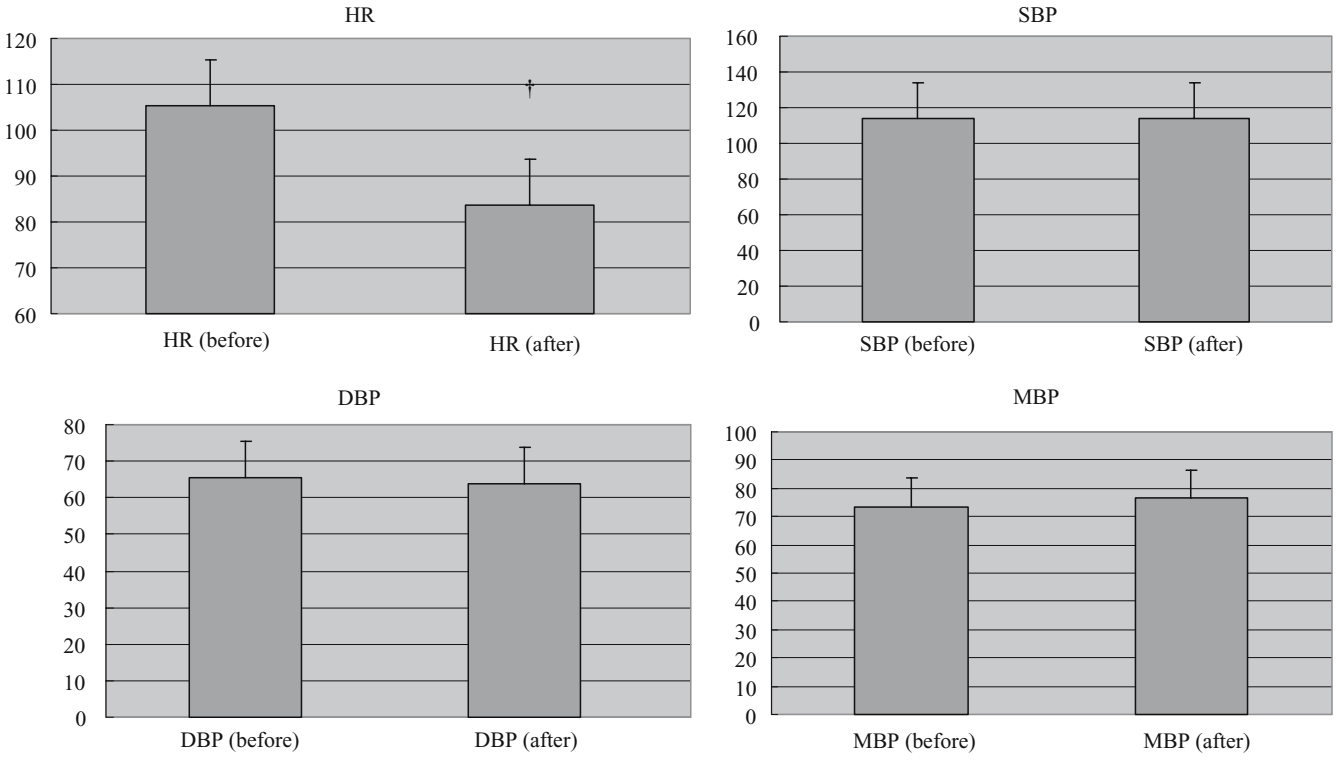

Fig. 1. Changes in vital signs before and after administration of landiolol. *HR*, heart rate (beats per min); *SBP*, systolic blood pressure (mmHg); *DBP*, diastolic blood pressure (mmHg); *MBP*, mean blood pressure (mmHg). $^{\dagger}P < 0.001$ using Wilcoxon signed-rank test

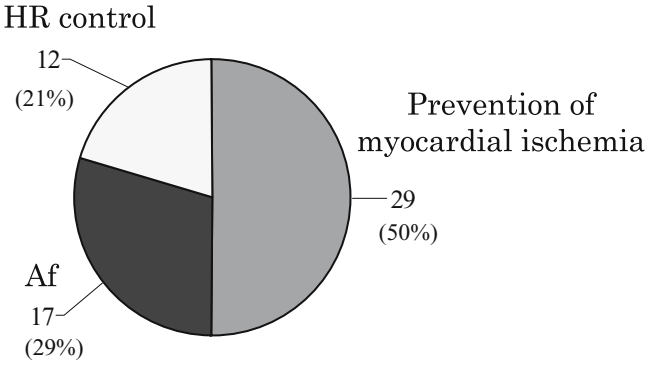

Fig. 2. Indications for landiolol (post-surgical patients). *Af*, atrial fibrillation; *HR*, heart rate

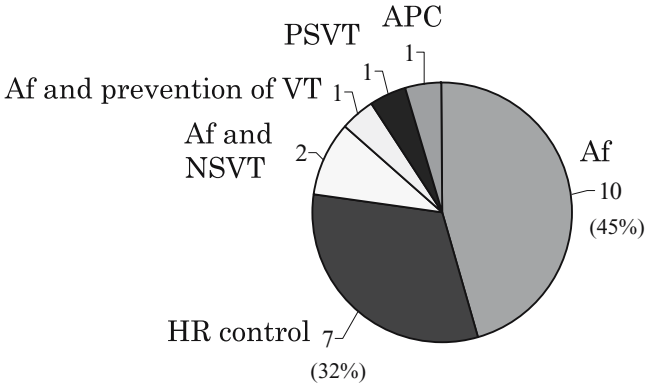

Fig. 3. Indications for landiolol (internal medicine patients). *Af*, atrial fibrillation; *HR*, heart rate; *NSVT*, nonsustained ventricular tachycardia; *VT*, ventricular tachycardia; *PSVT*, paroxysmal supraventricular tachycardia; *APC*, atrial paroxysmal contraction

patients with unstable hemodynamics because of its very rapid onset and offset of action. The regimen recommended on the packaging insert is a loading dose of 125 μg·kg^{-1}·min^{-1}, followed by a maintenance dose of 10–40 μg·kg^{-1}·min^{-1}, but we achieved the desired effect at a lower dose. Some other reports have also indicated that a lower dose of landiolol was effective [18–20]. In high-risk patients with hypertension and ischemic heart disease whose cardiac function and reserve is decreased, the beta-adrenergic blocking effect is stronger, and the frequency of low BP is increased [19–21]. It is thought that side effects such as a drop in BP can be decreased by the administration of a lower dose of landiolol.

The use of perioperative beta-adrenergic receptor blockers is well known to be useful to reduce myocardial ischemia [22–29], control tachycardia [18–21,30], and suppress arrhythmias [4–9]. Controlling these

Table 4. Catecholamine use and change in HR

	Catecholamine (+) (n = 63)		Catecholamine (–) (n = 17)	
	Before	After	Before	After
HR (BPM)	102.4 ± 23.4	84.4 ± 9.1	114.4 ± 20.5	85 ± 7.2
P value	<0.001		0.001	

HR, heart rate; BPM, beats per min

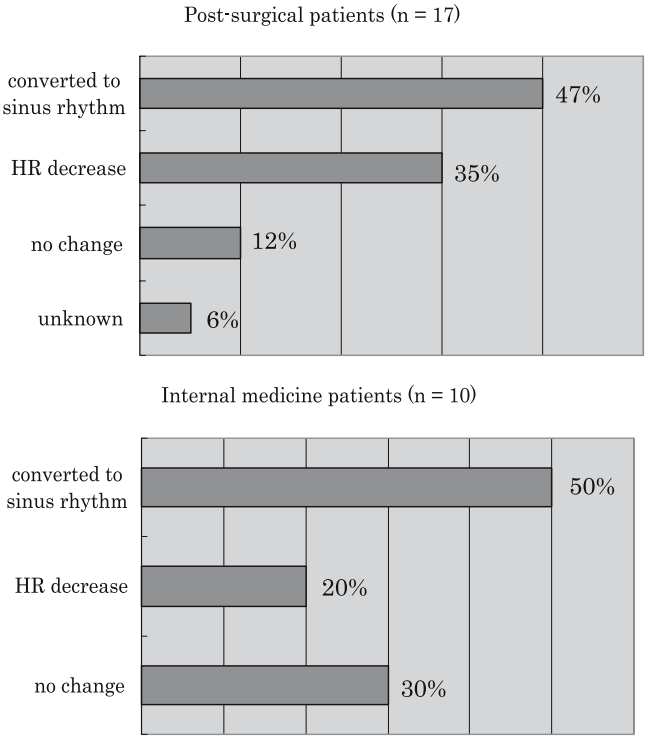

Fig. 4. Outcome for Af patients. *Af*, atrial fibrillation; *HR*, heart rate

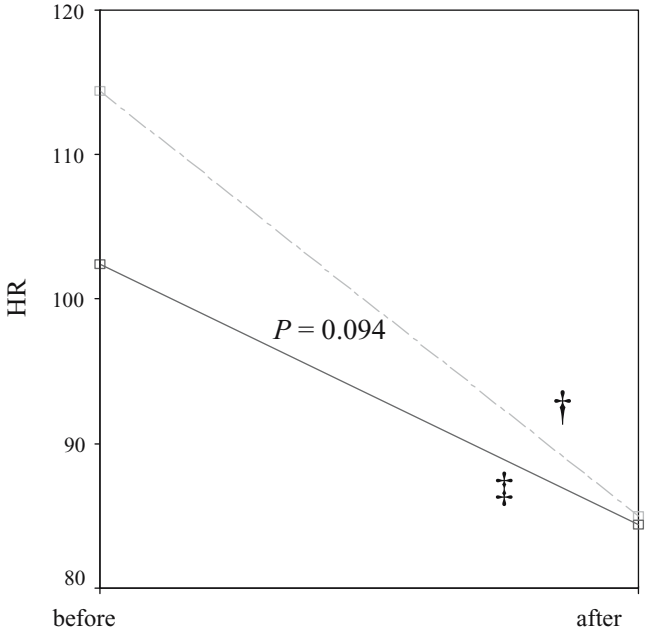

Fig. 5. The influence of catecholamine administration on heart rate (*HR*). *Continuous line*, catecholamine; *dashed* line, no catecholamine $^{\dagger}P < 0.001$ using Wilcoxon signed-rank test; $^{\ddagger}P = 0.001$ using Wilcoxon signed-rank test; $P = 0.094$ using Greenhouse-Geisser epsilon

factors stabilizes hemodynamics and facilitates recovery, and may also be important when considering treatment costs [31]. In this retrospective review, landiolol was used to prevent myocardial ischemia (50% of group S), to control HR (21% of group S and 32% of group IM), and as an anti-arrhythmic drug (29% of group S and 68% of group IM) (Figs. 2 and 3).

We used landiolol in four patients with cardiogenic shock and did not observe any further hemodynamic deterioration in these patients. Terajima [32] recently documented the effective use of landiolol in a patient with cardiogenic shock following AMI. The patient's cardiac output had decreased due to tachyarrhythmia in spite of an intraaortic balloon pump and a left ventricular assist system. Landiolol ($10\,\mu g \cdot kg^{-1} \cdot min^{-1}$) decreased HR from 136 to 96 beats per min (sinus rhythm), increased cardiac output from 2.3 to $2.5\,l \cdot min^{-1}$, decreased pulmonary capillary wedge pressure from 25 to 22 mmHg, and increased stroke volume from 18 to 22 ml [32]. We have also previously reported the successful management of a septic shock patient using landiolol [18]. Although beta-adrenergic receptor blockers were thought to be contraindicated for patients with shock patients, we think that landiolol may be used safely in these patients if it is carefully titrated with continuous hemodynamic monitoring.

ICU patients have unstable circulatory dynamics and may be unable to take oral medication. The pharmacokinetics of drugs taken orally is also difficult to predict. For these reasons, intravenous drugs with rapid onset and offset of action are desirable for ICU patients. When beta-adrenergic receptor blockers are required for ICU patients, intravenous administration is preferable to oral, especially during the perioperative period. Following cardiovascular operations and other very invasive operations such as esophagectomy, circulatory

kinetics is very unstable. ICU staff need to carefully titrate cardiovascular drugs intravenously, as it is difficult to predict their efficacy and pharmacokinetics. Following gastrointestinal operations and CABG surgery using the right gastric artery, patients are unable to take anything orally for a certain period. Discontinuation of beta–adrenergic receptor blockers can sometimes induce a withdrawal syndrome [33]. Therefore, landiolol is valuable as a bridge to resuming oral beta-adrenergic receptor blockers.

There are several potential limitations to our study because of its retrospective design. The effects of other drugs and medications could not be ruled out. Landiolol was used in group IM patients when other anti-arrhythmic drugs could not control HR, or when the patients were hemodynamically unstable. Many group S patients received catecholamines. However, we did not detect any problems with the combined administration of other drugs with landiolol. Although our retrospective review indicates that landiolol is valuable for anti-arrhythmic therapy and the prevention of myocardial ischemia in the ICU, a prospective study and evaluation of long-term prognosis are needed to determine the efficacy of landiolol in ICU patients.

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