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Safety and Efficacy of an Ultrashort-Acting β1-Blocker on Left Ventricular Dysfunction

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ABSTRACT

Landiolol hydrochloride, an ultrashort-acting β1-selective blocker, is a highly regulated drug. This study evaluated the safety and efficacy of this drug for cases of coronary artery bypass grafting (CABG) with left ventricular dysfunction. Between September 2006 and August 2009, 32 patients with a left ventricular ejection fraction of <40% underwent CABG. Two groups of patients, a group administered landiolol hydrochloride and a control group not administered this drug, were compared. The administration of landiolol hydrochloride was initiated at 1 μg/kg per minute (γ) after cardiopulmonary bypass in on-pump cases and after completion of all the distal anastomoses in off-pump cases. We observed no significant differences between the groups with respect to preoperative patient background or incidences of complications, except for postoperative atrial fibrillation. The heart rate decreased significantly 30 minutes after landiolol hydrochloride administration, but no change was observed in arterial pressure. No change was observed in other parameters; the hemodynamics were stable. The occurrence of atrial fibrillation during the intensive care unit stay (during landiolol hydrochloride administration) was significantly lower in the administration group. The difference remained significant after multiple logistic regression analysis; landiolol hydrochloride was the sole inhibitory factor.

INTRODUCTION

The appearance of tachyarrhythmia, such as atrial fibrillation, during the perioperative period increases myocardial oxygen consumption and deteriorates the patient's hemodynamics. Furthermore, it is considered a risk factor for myocardial ischemia, because the shortened left ventricular diastolic time decreases coronary artery blood flow [Slogoff 1985, 1988]. Therefore, it is particularly important to control tachyarrhythmia during the perioperative period in cases of coronary artery bypass grafting (CABG). The American College of Cardiology and American Heart Association (ACC/AHA) guidelines state that the administration of a β-blocker during the early postoperative period in patients without β-blocker contraindications should be the standard treatment (class I) to prevent atrial fibrillation and decrease its continuation [Eagle 2004], thus promoting the early administration of a β-blocker following CABG surgery. Some reports indicate, however, that administration of a β-blocker deteriorates hemodynamics [Aleksic 2000; Kurian 2001]. Therefore, its administration has tended to be avoided, particularly in patients with left ventricular dysfunction. Landiolol hydrochloride, which is an ultrashort-acting β-blocker, was developed in Japan as a drug with a short half-life, very high β1 selectivity, and good regulation. In the present study, we studied not only the safety and efficacy of landiolol hydrochloride for patients with left ventricular dysfunction but also the suitability of the administration method. Its influence on the occurrence of postoperative atrial fibrillation was simultaneously determined.

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MATERIALS AND METHODS

Among the 263 consecutive CABG surgeries performed between September 2006 and August 2009, 32 patients with a left ventricular ejection fraction of <40% according to echocardiography or left ventriculography evaluation but who had no chronic atrial fibrillation, pacemaker, or implanted cardioverter defibrillator were enrolled as participants (number of male/female participants, 27/5; mean (±SD) age, 63.2 ± 11.0 years; range, 42-85 years).

Landiolol hydrochloride was added to the normal treatment of 16 patients from June 2008 to August 2009 (landiolol group), and this group of patients was compared with 16 patients from September 2006 to May 2008 who were not administered landiolol hydrochloride (control group).

Fentanyl and sevoflurane were used for anesthesia induction. The upper limit of the total amount of fentanyl was 20 μg/kg, with sevoflurane concomitantly used. Propofol was used for maintenance and was administered at 3 mg/kg per hour.

The administration of landiolol hydrochloride was initiated at 1 μg/kg per minute (γ) at the end of cardiopulmonary bypass in on-pump cases and after completion of distal anastomoses in off-pump cases. It was increased by 1-γ increments so that the target heart rate (HR) became 90 beats/min. The minimum dose was 1 γ, and this dose was used during the intensive care unit (ICU) stay. A discontinuation criterion was excessive reduction in blood pressure that did not improve with other inotropic agents. Perioperative hemodynamic monitoring included continuous γ measurement in relation to the HR, mean arterial pressure, pulmonary artery pressure, pulmonary capillary wedge pressure, and central venous pressure. Thermodilution cardiac output was measured with a flow-directed pulmonary artery catheter connected to a cardiac output computer and injection of 5 mL ice-cold 0.9% saline. Derived hemodynamic data (stroke volume index, cardiac index, systemic vascular resistance index, and pulmonary vascular resistance index) were calculated with standard formulas. Hemodynamic data were obtained before starting the infusion of the study drug, after 30 minutes, at the end of the surgery, and at 1 and 2 days after surgery. Five-lead automated continuous electrocardiographic monitoring for ischemia detection started with the induction of anesthesia and continued until the patient left the ICU.

Postoperative atrial fibrillation was observed via a continuous electrocardiographic monitor or a 12-lead electrocardiogram. Postoperative atrial fibrillation was defined as a lack of P waves before the QRS complex that continued for 30 minutes and having an irregular heartbeat. Continuation for <30 minutes but requiring treatment, such as further administration of antiarrhythmic drugs and countershock, was also considered postoperative atrial fibrillation.

Data are presented as the mean ± SD, and the Shapiro-Wilk test was used as a test for data normality. Classification data for the landiolol and control groups were analyzed with the χ^2 test or the Fisher exact test. Continuous variables were analyzed with an unpaired Student t test or the Mann-Whitney *U* test. Changes in hemodynamics during landiolol hydrochloride administration were compared with repeated-measures one-way analysis of variance, and the Bonferroni test was used as a nonparametric method. *P* values <.05 were considered statistically significant.

In addition, a multivariate analysis of factors associated with the occurrence of postoperative atrial fibrillation was performed according to a logistic regression model. For all tests, SPSS software (version 18.0 for Windows; SPSS/IBM, Chicago, IL, USA) was used.

Table 1. Patient Characteristics*

	Landiolol Group (n = 16)	Control Group (n = 16)	*P*
Age, y	64.2 ± 11.0	62.3 ± 11.3	.375
Male/female sex, n	12/4	15/1	.166
Preoperative medication, n			
β-Blocker	9	7	.480
Statin	13	10	.217
Angiotensin-converting enzyme inhibitor	1	2	.500
Cardiac risk factor, n			
Hypertension	11	9	.465
Diabetes mellitus	11	11	.648
Hyperlipidemia	12	11	.500
History of cerebrovascular disease	3	2	.500
Renal dysfunction†	4	9	.072
Smoking	10	9	.719
Peripheral arterial disease	4	5	.500
Old myocardial infarction	6	11	.077
Congestive heart failure	13	13	.673
Left ventricular ejection fraction, %	32.4 ± 7.6	29.6 ± 6.1	.257
No. of diseased vessels	2.9 ± 0.3	2.8 ± 0.6	.279
EuroSCORE	6.0 ± 4.4	7.6 ± 3.1	.063

*Data are expressed as the mean ± SD or as the number of patients.
†Serum creatinine >1.5 mg/dL.

Table 2. Data from the Perioperative Period*

	Landiolol Group (n = 16)	Control Group (n = 16)	*P*
Type of operation, n			.028
CABG without valve procedures	13	7	
CABG with valve procedures	3	9	
Total operative time, h	6.8 ± 2.1	7.6 ± 2.1	.203
Cardiopulmonary bypass time, min	208 ± 77 (n = 5)	225 ± 82 (n = 12)	.695
Cross-clamp time, , min	128 ± 63 (n = 3)	112 ± 52 (n = 9)	.685
No. of distal coronary anastomoses per patient	4.4 ± 1.1	3.9 ± 1.4	.349
Intraoperative blood loss, g	462 ± 240	419 ± 138	.534
Transfusion, n	13	13	.673

*Data are expressed as the mean ± SD or as the number of patients. CABG indicates coronary artery bypass grafting.

RESULTS

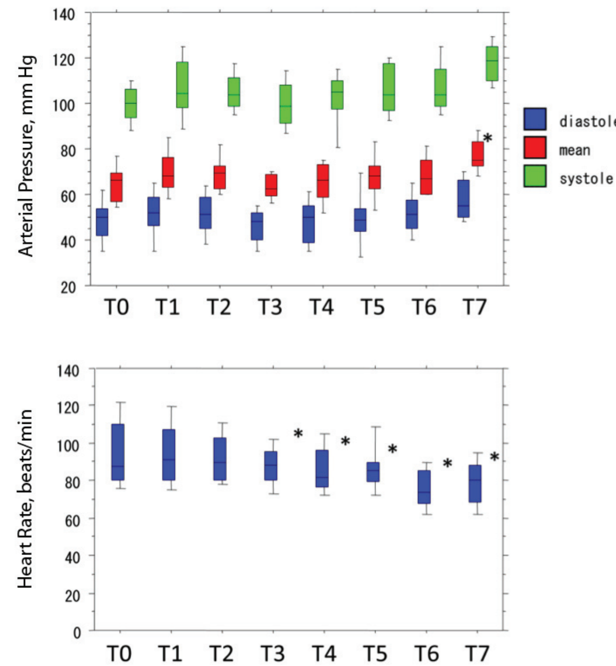
Patient Characteristics and Perioperative Factors

The patients' preoperative characteristics are listed in Table 1. The mean age was 64.2 ± 11.0 years in the landiolol group and 62.3 ± 11.3 years in the control group, with males constituting 75.0% and 93.8% of the patients, respectively (hereafter, data for the groups will be presented in the following format: landiolol group/control group). No differences were observed between the groups with respect to preoperative coronary risk factors and preoperative oral treatment. In addition, no significant differences were observed with respect to the number of diseased vessels, the left ventricular ejection fraction, or the EuroSCORE, which were 2.9 ± 0.3/2.8 ± 0.6, 32.4% ± 7.6%/29.6% ± 6.1%, and 6.0 ± 4.4/7.6 ± 3.1, respectively. Perioperative factors are listed in Table 2. The rate of valve procedures was significantly higher in the control group (18.8%/56.3%; P = .028); however, no significant differences were observed in the operative times (6.8 ± 2.1 hours/7.6 ± 2.1 hours), the number of distal coronary anastomoses (4.4 ± 1.1/3.9 ± 1.4), and cardiopulmonary bypass times (208 ± 77 minutes/225 ± 82 minutes). Furthermore, no significant differences were observed between the groups with respect to blood loss (462 ± 240 g/419 ± 138 g) and transfusion rate (13%/13%).

Table 3. Postoperative Morbidity and Mortality Data*

	Landiolol Group (n = 16)	Control Group (n = 16)	*P*
ICU stay, d	2.6 ± 1.2 (1-5)	4.9 ± 4.2 (1-16)	.193
Hospital stay, d	23.6 ± 8.0 (15-48)	35.6 ± 27.6 (12-125)	.111
Mediastinitis, n	0	1	.500
Perioperative myocardial infarction, n	0	0	—
Cerebrovascular accidents, n	1	0	.500
Reexploration for bleeding, n	0	1	.500
Early death (<30 d), n	0	0	—
Hospital death, n	1	1	.758

*Data are expressed as the mean ± SD and range or as the number of patients. ICU indicates intensive care unit.



Changes in blood pressure (top panel) and heart rate (bottom panel) after initiation of landiolol administration. Heart rate decreased significantly 30 minutes after initiating administration without a concomitant change in the arterial pressure. T0, initiation; T1, 10 minutes; T2, 20 minutes; T3, 30 minutes; T4, 60 minutes; T5, end; T6, 1 day after surgery; T7, 2 days after surgery. Data are presented as the mean SD and range. *P < .05.

Postoperative Morbidity

The number of postoperative ICU days and the number of hospitalization days tended to be low in the landiolol group (Table 3). Hospital death was observed in both groups. No cases of early death were observed, however, and the incidences of major complications in the 2 groups were equivalent, except for postoperative atrial fibrillation.

Changes in Hemodynamics in the Landiolol Group

HR decreased immediately after landiolol administration (94.3 ± 18.4 beats/min) and decreased significantly 30 minutes later, compared with the HR before administration (P = .014) (Figure, Table 4). The arterial pressure did not change,

Table 4. Perioperative Hemodynamic Data*

Time Group	CVP, mm Hg	MPAP, mm Hg	PCWP, mm Hg	SVI, mL/m^2	CI, L/mL per m^2	PVRI, dyns^{-1}cm^{-5}m^{-2}	SVRI, dyns^{-1}cm^{-5}m^{-2}
Before study	7.7 ± 1.6	18.0 ± 3.0	10.1 ± 2.3	33.6 ± 8.3	3.2 ± 0.7	211 ± 101	1539 ± 367
After 30 min	9.6 ± 2.5	18.9 ± 4.0	11.7 ± 2.6	31.3 ± 7.7	3.0 ± 1.0	207 ± 88	1810 ± 619
End of surgery	9.1 ± 3.0	19.7 ± 4.4	13.5 ± 4.0	36.0 ± 8.0	3.1 ± 8.0	173 ± 95	1841 ± 671
1 Day after surgery	10.6 ± 2.7	18.6 ± 4.5	13.3 ± 3.6	35.5 ± 9.8	2.7 ± 0.7	155 ± 41	1769 ± 510
2 Days after surgery	7.8 ± 3.5	17.1 ± 4.2	11.6 ± 4.1	34.7 ± 9.4	2.9 ± 0.8	19 ± 50	1951 ± 864

*CVP indicates central venous pressure; MPAP, mean pulmonary artery pressure; PCWP, pulmonary capillary wedge pressure; SVI, stroke volume index; CI, cardiac index; PVRI, pulmonary vascular resistance index; SVRI, systemic vascular resistance index.

however. No difference was observed in the stroke volume index or the cardiac index, which are derived hemodynamic data, and no changes were observed in the central venous pressure, pulmonary vascular resistance index, systemic vascular resistance index, or pulmonary capillary wedge pressure, which are preload and afterload indices for both ventricles.

Table 5. Multiple Logistic Regression Analysis of Postoperative Atrial Fibrillation after Coronary Artery Bypass Grafting

Coronary Artery Bypass Grafting	Odds Ratio*	*P*
Landiolol hydrochloride	0.091 (0.009-0.969)	.047
Age	0.851 (0.739-0.981)	.026
Hypertension	0.238 (0.028-2.007)	.187

*Odds ratios are presented with the 95% confidence interval in parentheses.

Occurrence of Atrial Fibrillation

The incidence of postoperative atrial fibrillation during the ICU stay was 31.3%. Univariate analysis was performed in the occurrence and nonoccurrence groups (Table 5). As analysis variables, we used preoperative and postoperative oral treatment (β-blocker, statin, angiotensin-converting enzyme inhibitor), sex, age, hypertension, renal dysfunction, chronic obstructive pulmonary disease, left atrial diameter, left ventricular ejection fraction, EuroSCORE, and with/without valve procedures. Significant differences were observed with respect to age (P = .001) and administration of landiolol hydrochloride (P = .022). Multivariate analysis was performed on these variables. The administration of landiolol hydrochloride (odds ratio [OR], 0.091; 95% confidence interval [CI], 0.009-0.969; P = .047) and advanced age (OR, 0.851; 95% CI, 0.739-0.981; P = .026) were postoperative factors inhibitory for atrial fibrillation. Moreover, in a similar study that investigated atrial fibrillation occurrence 1 week after surgery, only landiolol hydrochloride was associated with postoperative atrial fibrillation (OR, 0.126; 95% CI, 0.018-0.875; P = .036).

DISCUSSION

Atrial fibrillation is one of the most frequent complications after cardiac surgery, occurring in 25% to 40% of cases [Hashimoto 1991; Aranki 1996; Ommen 1997]. Postoperative atrial fibrillation is considered to be due to thromboembolism and leads to extended ICU and hospital stays, in addition to increased medical costs [Hogue 2005].

Moreover, tachyarrhythmia is the most common type of atrial fibrillation, which increases myocardial oxygen consumption. It is also considered a risk factor for myocardial ischemia, because a shortened left ventricular diastolic time decreases coronary artery blood flow [Slogoff 1985, 1988]. Atrial fibrillation can be a serious problem, particularly after CABG. In recent years, there have been many reports regarding therapeutic [Martinez 2005] and prophylactic [Coleman 2004; Mathew 2004] administration of β-blockers for postoperative atrial fibrillation after cardiac surgery, and β-blockers have largely contributed to the improvement in postoperative results. The ACC/AHA guidelines also state that administration of a β-blocker during the early postoperative period to a patient with no contraindications should be the standard treatment (class I) for preventing atrial fibrillation and decreasing its continuation [Eagle 2004]; thus, these guidelines promote early administration of a β-blocker following CABG.

The efficacy of β-blockers is wide-ranging and includes many effects. Their versatility includes the following: inhibiting the production of inflammatory cytokines that promote cardiac failure [Bristow 2000; Prabhu 2000]; an interleukin 6–decreasing effect in patients with hypertrophic obstructive cardiomyopathy [Ohtsuka 2002]; protection of organs and an anti-inflammatory effect when used concomitantly with the phosphodiesterase III inhibitor enoximone [Boldt 2004]; decrease in myocardial ischemia and improvement of heart function [Suttner 2009]; and inhibition of pain with intraspinal administration [Zhao 2007].

Reports regarding the various effects of β-blockers also have often described hemodynamic deterioration [Aleksic 2000; Kurian 2001]. In addition, drugs had also previously been associated with poor regulation and blood pressure reduction, and their use in other surgical fields was difficult [Bayliff 1999]. β-Blockers can be fatal, particularly in cases of left ventricular dysfunction; therefore, discovery of a new -blocker was desired.

Esmolol, a short-acting β1-selective blocker, was approved by US Food and Drug Administration in 1986 for the treatment of supraventricular tachycardia and was additionally used beginning in 1992 to treat perioperative and postoperative tachycardia and hypertension. Esmolol was claimed to reduce the side effects of propranolol hydrochloride, which had been the most commonly used drug until then but was nonselective and long acting. Esmolol was appreciated, particularly in the field of anesthesiology, for its inhibitory effect on changes in hemodynamics at the time of anesthesia induction and ventilator weaning [Fernandez-Galinski 2004; Arar 2007], for its effect in reducing pain at the time of administration of muscle-relaxant drugs [Yavascaoglu 2007], and for decreasing the amount of administered anesthetic agent [Johansen 1997; Wilson 2004]. Esmolol has a disadvantage, however, in that a high dose is required to reach the therapeutic range, because its activity is lower than that of conventional β-blockers.

Landiolol hydrochloride, used in the present study, is an ultrashort-acting β1-selective blocker similar to esmolol. It was developed in Japan and has been used as an agent for treating tachyarrhythmia during surgery since 2002 [Kinoshita 2005]. Landiolol hydrochloride is characterized by a serum half-life of approximately 4 minutes, indicating excellent regulation, high β1 selectivity, and high activity (the β-blocking action was approximately 9 times as high as that of esmolol in in vivo experiments with dogs). In addition, landiolol possesses a cardioselectivity that is approximately 8 times as high as that of esmolol, according to in vitro experiments that used right atrial tissue from pigs [Iguchi 1992]. Furthermore, landiolol hydrochloride has been demonstrated not to affect left ventricular preload and afterload, whereas esmolol increases the left ventricular preload [Sugiyama 1999], and landiolol's negative chronotropic effect is stronger than that of esmolol hydrochloride [Sasao 2001; Ikeshita 2008]. Changes in hemodynamics, such as the development of hypertension and tachycardia at the time of awakening from anesthesia and immediately after extubation [Hartley 1993], cause rapid oxygen demand in patients with coronary lesions and are highly dangerous. Therefore, we considered the necessity of stabilizing hemodynamics in conducting the present study.

Besides describing the effects of the inhibition of tachycardia and blood pressure elevation at the time of endotracheal intubation [Kitamura 1997; Goyagi 2005; Yamazaki 2005], inhibition of HR elevation and the bispectral index at the time of endotracheal intubation [Oda 2005], and HR stabilization at the time of awakening from anesthesia and extubation [Shirasaka 2008], reports on the use of landiolol hydrochloride have also described occasional observations of an effect on preventing myocardial ischemia [Kimura-Kurosawa 2007]. In cases of left ventricular dysfunction, however, there have also been reports claiming that landiolol could decrease both HR and cardiac output, as with conventional β-blockers [Goto 2010]. Therefore, there has been a tendency to refrain from using landiolol hydrochloride. The present study has demonstrated that landiolol hydrochloride can be used in a way such that only the negative chronotropic effect is achieved. The period between the initiation of administration and the onset of the effect was believed to depend on the length of the administration route; however, our results showed that landiolol hydrochloride could rapidly decrease only the HR without affecting the arterial pressure or the pulmonary arterial pressure. Furthermore, landiolol affected neither the preload nor the afterload of both ventricles. Therefore, our study elucidated that only the negative chronotropic effect can be obtained when properly established administration methods are used. We also conducted a study regarding the occurrence of postoperative atrial fibrillation. Among the factors (including advanced age, male sex, hypertension, left atrial diameter, renal dysfunction [Aranki 1996; Almassi 1997], and statin use) considered to be inhibitory for postoperative atrial fibrillation [Marín 2006] but previously considered risk factors for atrial fibrillation, we found that age and the administration of landiolol hydrochloride to be inhibitory factors. Postoperative atrial fibrillation in the group administered landiolol hydrochloride was observed in only 2 patients—one with paroxysmal atrial fibrillation before surgery and the other undergoing dialysis on day 1 after surgery. We note, however, that not only could atrial fibrillation be significantly inhibited during the administration of landiolol hydrochloride, but its occurrence within 1 week after surgery was also affected. Because the half-life of the drug is short, its effect after discontinuation is unknown, as is the mechanism for inhibiting atrial fibrillation within 1 week, but we believe that the fact that the drug decreases the HR during the acute period and consequently stabilizes hemodynamics leads to the inhibition of postoperative atrial fibrillation.

In the present study, the safety of landiolol hydrochloride and the suitability of the current administration methods were studied only in regard to left ventricular dysfunction. We believe the β-blocker would be safe and effective—particularly in cases of left ventricular dysfunction in which such administration is not currently used—if appropriate administration methods were devised. Therefore, we believe landiolol hydrochloride to have a stabilizing effect during the perioperative period. It is necessary, however, to increase the number of cases as well as to study the results during the follow-up period.

Limitations

There were some limitations associated with this study. First, our study was retrospective in nature and carried out at a single institution. The number of patients was small, because only isolated coronary surgery cases with a low left ventricular function were selected. Given that this drug has a very short half-life, the development of an administration method to minimize the occurrence of side effects is currently required. We consider the administration of landiolol hydrochloride to be safe when it is initiated at 1 μg/kg per minute (γ), and we experienced no major complications with this administration method. Further studies to evaluate this administration method at many institutions are thus important. In addition, randomized controlled trials will be necessary in the future.

CONCLUSIONS

In cases of left ventricular dysfunction, an ultrashort-acting β1-selective blocker can be safely used, and stable perioperative management can thereby be achieved. Moreover, landiolol hydrochloride was also found to inhibit postoperative atrial fibrillation.

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