Efficacy and Safety of Landiolol Compared to Amiodarone for the Management of Postoperative Atrial Fibrillation in Intensive Care Patients

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Objective: **The authors assessed the efficacy and safety of landiolol, an ultra–short-acting beta-blocker, with those of amiodarone in the restoration of sinus rhythm for postoperative atrial fibrillation (POAF) in intensive care unit (ICU) patients.**

Design: **A retrospective data analysis.**

Setting: **Data were collected from patients admitted to the ICU in a single university hospital between 2012 and 2015.**

Participants: **Records of a total of 276 patients who developed POAF after ICU admission were collected from hospital records.**

Interventions: **None.**

Measurements and Main Results: **Treatment success was defined as restoration of sinus rhythm without concomitant therapy within 24 hours of treatment and lasting for more than an hour. The landiolol dosage was in the range of 0.7 μg/kg/min-to-2.5 μg/kg/min. The authors compared a total of 55 patients with POAF who received either landiolol (n = 32) or intravenous amiodarone (n = 23) in the ICU. The major findings were that the median time required for conversion to sinus rhythm was shorter in landiolol patients compared with amiodarone patients (75 *v* 150 min respectively, p = 0.0355). However, treatment success rates did not differ significantly after 24 hours (odds ratio 1.25, 95% confidence interval 0.17-9.09, p = 0.60). Adverse events with bradycardia leading to drug discontinuation were seen only in the patients receiving amiodarone (n = 3, p = 0.032).**

Conclusions: **Landiolol achieved swift and safe restoration of sinus rhythm in ICU patients with POAF and could be considered as a favorable drug choice over amiodarone in such patients.**

KEY WORDS: postoperative atrial fibrillation, beta-blocker, landiolol, intensive care, amiodarone

THE OPTIMAL MANAGEMENT of newly developed atrial fibrillation (AF) in patients treated in the intensive care unit (ICU) during the early postoperative period is unclear.[1–3] Although many drug options exist for the pharmacologic management of AF, only a few are suited for intensive care settings. According to several guidelines concerning postoperative atrial fibrillation (POAF) after cardiac surgery, intravenous (IV) beta-blockers and amiodarone are both recommended for rate-control therapy. Amiodarone also can be used as an agent for pharmacologic cardioversion.[4,5] Whereas both IV treatments are used widely in the ICU, there is no clear evidence regarding which beta-blocker should be used and whether a particular beta-blocker is superior to amiodarone for rate control.

Currently, the cardioselective $beta_1$-blocker, esmolol, frequently is used in the ICU for the treatment of acute supraventricular arrhythmias. Although esmolol has become preferred over longer acting beta-blockers, it has been reported to exert a potent negative inotropic action and induce excessive hypotension in patients with poor cardiac function.[6]

Landiolol hydrochloride, another cardioselective "ultra-short-acting" $beta_1$-blocker, was developed in Japan. Compared with esmolol, landiolol has been shown to have a less potent negative inotropic effect and an 8-fold greater cardioselectivity ratio. In addition, landiolol has a short elimination half-life (t1/2) of 4 minutes, which is shorter than that of esmolol (t1/2 = 9 minutes). The landiolol elimination half-life is not affected by the dosage, allowing rapid recovery following the cessation of drug administration.[7] Since its release, landiolol has become widely used in Japan for the emergency management of POAF, and its potential usefulness for the prevention of POAF after cardiac surgery has been suggested.[8–10] Furthermore, studies that evaluated both esmolol and landiolol found both drugs to effectively accelerate the conversion to sinus rhythm in patients with POAF.[11–13]

The authors conducted a retrospective review of ICU patients who developed POAF and had received either landiolol or IV amiodarone for rate-control therapy. They aimed to evaluate the efficacy of both drugs with respect to the time required for POAF conversion to normal sinus rhythm, the rate of conversion, and side effects.

METHODS

After obtaining institutional ethical approval, the authors retrospectively created a list of patients who had received either amiodarone or landiolol at their institution between April 2012 and March 2015 by reviewing billing information. Based on this list, a comprehensive database was created from the hospital records of patients who had received either drug for rate-control therapy in the ICU.

DATA COLLECTION

The collected data included the preoperative demographic variables of age (years), sex, height (cm), and weight (kg); the presenting diagnosis; laboratory test results, incidence of newly developed AF after ICU admission; treatment for AF; whether normal sinus rhythm was restored within 24 hours after treatment (yes or no); and the time required for conversion to sinus rhythm after drug administration. Patients were excluded from the authors' analysis if they were heart transplant recipients or if any of the following factors were observed: failure to adhere to the institutional drug dosing protocol, age <20 years, acute myocardial infarction within 72 hours, prior history of arrhythmia, use of

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beta-blockers for rate control during cardiac procedures, diagnosis of a second- or third-degree atrioventricular block, permanent pacemaker implantation, hyperthyroidism, cardiomyopathy, or implantation of ventricular assist devices. Potassium levels were monitored and corrected if necessary at 5-hour intervals during the patients' stays in the ICU.

The authors' institutional dosing protocol was as follows: initiation of IV amiodarone with a loading dose infusion of 150 mg over 30 minutes (min), followed by a continuous infusion of 20 mg/h-to-50 mg/h, or initiation of IV landiolol with a bolus dose of 0.3 mg/kg, followed by a continuous infusion at an initial rate of 0.7 μg/kg/min, which was increased according to the patient's condition to a maximum of 2.5 μg/kg/min. After the initial continuous landiolol infusion rate was established, the dosage remained constant for 24 hours. Drug therapy was provided in the ICU under continuous electrocardiographic and direct arterial blood pressure monitoring in all patients. Data were acquired every 5 minutes.

OUTCOME MEASURES

From the authors' database, they compared the effectiveness of single-drug amiodarone or landiolol administration in terms of conversion to normal sinus rhythm. Their primary outcome was the time required for conversion to sinus rhythm after the administration of either landiolol or amiodarone. Treatment was considered successful if conversion to sinus rhythm was achieved within 24 hours (1,440 minutes) after drug administration and sustained for more than 60 minutes. Cases were censored if a second antiarrhythmic drug was added or electrical cardioversion was attempted before successful conversion to sinus rhythm. The secondary outcomes included the rate of conversion to sinus rhythm after 24 hours, recurrence of AF during continuous infusion (yes/no), and successful heart rate control (below 120/min). Any adverse reactions, including hypotension, that required treatment (systolic blood pressure <80 mmHg), bradycardia (heart rate <50/min), asystole, and atrioventricular block, also were recorded.

STATISTICAL ANALYSIS

Continuous data are expressed as medians with interquartile ranges. The Wilcoxon-Mann-Whitney signed-rank test was used to compare continuous variables and variables with skewed distributions. Categorical variables were compared using the chi-square test.

To compare the effectiveness of both drug treatments on the time required for POAF conversion to normal sinus rhythm, the authors used a time-to-event analysis. The probability of successful sinus rhythm conversion and the estimated median conversion times were determined through Kaplan–Meier analyses. The log-rank test was used for intergroup comparisons. A p value < 0.05 was considered statistically significant. Analyses were performed using Microsoft Excel® (version 2010, Microsoft Corporation, Redmond, WA) and JMP Pro 11® software (SAS Institute, Cary, NC).

RESULTS

Within the study period, a total of 276 patients had received either landiolol (n = 160) or amiodarone (n = 116) for rate control during their ICU stays. Based on the authors' inclusion criteria, 32 patients were included in the landiolol group and 23 were included in the amiodarone group for further analysis. There were no significant differences between the groups with respect to age, sex, body mass index, or time of AF onset (Table 1). The types of surgery were similar in both groups.

An inverse Kaplan–Meier analysis revealed that patients who received landiolol for single-drug rate control converted to sinus rhythm significantly sooner than did those receiving amiodarone (Fig 1) (log-rank test, $p = 0.0355$). The calculated median times to conversion were 75 and 150 minutes for the landiolol and amiodarone groups, respectively.

Conversion to sinus rhythm was successful in 18 and 10 cases in the landiolol and amiodarone groups, respectively (Table 2). Data were censored in 14 cases in the landiolol group for the following reasons: administration of a second drug, 9 patients; direct-current conversion, 2 patients; drug discontinuation due to side effects (both hypotension), 2 patients; and failure to achieve sinus conversion within 24 hours, 1 patient. Data were censored in 13 patients in the amiodarone group for the following reasons: administration of a second drug, 3 patients; direct-current conversion, 7 patients; and drug discontinuation following adverse events (hypotension with bradycardia), 3 patients.

Landiolol and amiodarone did not differ significantly in their abilities to effectively maintain sinus rhythm for 24 hours after the initial single drug treatment (odds ratio = 1.25, 95% confidence interval: 0.17-9.09, $p = 0.60$). In the landiolol group, recurrences of AF after sinus conversion occurred in 1 patient each with valvular replacement, valvular replacement and coronary artery bypass grafting (CABG), and CABG. In the amiodarone group, recurrences of AF after sinus conversion involving CABG occurred in 2 patients.

Regarding side effects, bradycardia within 60 minutes after infusion was not recorded in any patients in the landiolol group, whereas this side effect occurred in 3 patients in the amiodarone group. The incidence rates of hypotension and failure to control heart rate were similar in both groups (Table 2).

DISCUSSION

The present study described the accelerated conversion of POAF to normal sinus rhythm with the use of landiolol when

Table 1. Clinical Characteristics of the Study Patients

	Landiolol n = 32	Amiodarone n = 23	p Value
Age (years)	72.5 (66, 78)	68 (60, 76)	0.11
Sex (F/M)	11/21	7/16	0.76
BMI	23.8 (20.8, 27.5)	22.1(19.5, 25.7)	0.28
Onset (postoperative days)	3 (2, 4)	3 (2, 4)	0.40
Type of surgery			
CABG	13 (40.6 %)	8 (34.8 %)	
CABG + VR	4 (12.5 %)	4 (17.4 %)	
VR	14 (43.8 %)	9 (39.1 %)	
V	1 (3.1 %)	2 (8.7 %)	

NOTE. Values are listed as medians (25th, 75th interquartile ranges) or as numbers (percentages) where appropriate.

Abbreviations: BMI, body mass index; CABG, coronary artery bypass grafting; V, vascular surgery; VR, valve replacement.