Showa Univ J Med Sci **31**(3), 275～281, September 2019

Original

Effects of the Prophylactic Use of Amiodarone Infusion to Prevent Postoperative Atrial Fibrillation after Cardiac Surgery

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Abstract: Postoperative atrial fibrillation (AF) is associated with significant morbidity after cardiac surgery. We examined the effects of a prophylactic postoperative amiodarone infusion to prevent postoperative AF. A prospective randomized study was performed in patients with a high risk of postoperative AF between March 2016 and March 2019. High risk of AF was defined as combined valve surgery, aortic valve replacement (age > 70), or off-pump coronary bypass grafting (age > 65). Forty-two patients were enrolled and randomly assigned to receive prophylactic amiodarone infusion (amiodarone group, n = 20) or saline infusion (control group, n = 22). In the amiodarone group, amiodarone was infused intravenously for 48 hr postoperatively (initially 125 mg/10 min, then 288 mg/6 hr, then maintenance of 1,040 mg/42 hr). There were no significant differences between the two groups in age, sex, body height, body weight, surgical procedure, and perioperative use of beta blockers. The occurrence of sustained AF for > 1 hr was significantly lower in the amiodarone group (30.0%) than in the control group (63.6%, $p = 0.04$). The total duration of AF over one week was also significantly shorter in the amiodarone group (296.8 ± 676.9 min) than in the control group (921.4 ± 1641.6 min, $p = 0.04$), as was the postoperative hospital stay (17.3 ± 6.1 vs. 24.5 ± 11.3 days, respectively, $p = 0.01$). There were no major side effects with amiodarone infusion except for one case of bradycardia. These results show the prophylactic use of intravenous amiodarone infusion for the first 48 hr of the postoperative period is a safe and effective treatment to prevent postoperative AF after cardiac surgery and to shorten the hospital stay.

Key words: amiodarone, postoperative atrial fibrillation, cardiac surgery

Introduction

Postoperative atrial fibrillation (AF) has an incidence of 30%–50% after cardiac surgery[1–3]. Postoperative AF occurs most frequently on postoperative day two and recurs 40% of the time[4, 5]. Postoperative AF is associated with increased morbidity and mortality and longer, more expensive hospital stays[6–8].

The American Heart Association / American College of Cardiology / Heart Rhythm Society

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guidelines have already recommended the preoperative administration of amiodarone to reduce the incidence of AF (Class IIa)[9]. Furthermore, several clinical studies have evaluated the preoperative use of amiodarone (oral and intravenous use) for the prevention of postoperative AF[10–19]; however, a disadvantage of this method is that it requires intensive monitoring for the occurrence of bradycardia caused by amiodarone use.

An advantage of the postoperative use of intravenous amiodarone for 48 hr is that postoperative AF occurs most frequently on postoperative day two[4,5]; thus, the concentration of amiodarone would be in the effective range during this period. Furthermore, because a temporary pacing wire is routinely implanted on the right ventricle during the operation, bradycardia caused by amiodarone infusion can be safely managed by temporary pacing in the intensive care unit (ICU). Consequently, there is less additional burden for perioperative care due to postoperative prophylaxis compared with preoperative amiodarone use.

The aim of this study was to clarify whether intravenous amiodarone administration only during the immediate 48 hr post-surgery period is effective for the prevention of postoperative AF.

Patients and methods

This study was approved by the Institutional Review Board of the Showa University Hospital (Permit Number: 1451081).

This prospective randomized study was conducted between March 2016 and March 2019. The 154 patients who underwent open cardiac surgery during this period were screened, and 132 of these patients had elective operations. Sixty-five patients were excluded due to prior AF ($n=49$), pacemaker implantation ($n=5$), sick sinus syndrome ($n=1$), complete left bundle branch block ($n=1$), or hemodialysis ($n=9$). We selected high-risk patients for our cohort according to previous studies to prove the effectiveness of our procedure. Several preoperative factors including age, dilatation of the left atrium, and left ventricular hypertrophy carry high associations with the occurrence of postoperative AF; likewise, some intraoperative factors such as surgical or ischemic injuries to the atrium and pulmonary veins caused by cannulation have high associations[20,21]. Therefore, combined valve surgery was considered to have a high risk of postoperative AF, in addition to aortic valve replacement and off-pump coronary bypass grafting in elderly patients. High risk of AF was defined as combined valve surgery, aortic valve replacement (>70 years old), or off-pump coronary bypass grafting (>65 years old). Forty-four of the eligible patients were classified in the high-risk AF group. Two patients refused to enroll in the study. The remaining 42 patients gave both verbal and written consent to participate in the trial. They were randomly divided into two groups: amiodarone group ($n=20$) and control group ($n=22$) (Fig. 1). For the patients in the amiodarone group, amiodarone was infused intravenously for 48 hr at the following rates: initial rapid infusion (125 mg/10 min), loading dose (288 mg/6 hr), and maintenance dose (1,040 mg/42 hr); administration began just after transportation to the ICU after surgery.

We used 24-hr continuous electrocardiogram monitoring during the first postoperative week

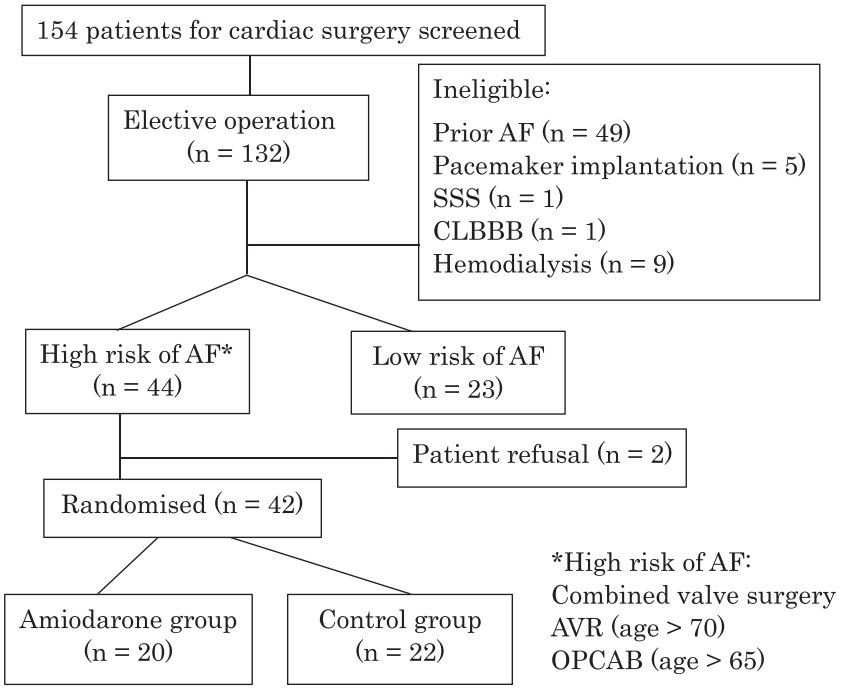

Fig. 1. Study flowchart. AF: atrial fibrillation, SSS: sick sinus syndrome, CLBBB: complete left bundle branch block, AVR: aortic valve replacement, OPCAB: off-pump coronary artery bypass

and defined AF as a continuous AF waveform for more than 5 min. The occurrence of sustained AF for more than one hr, total duration of AF over one week, postoperative hospital stay period, and required treatments were compared between the two groups. We used Fisher's exact test for categorical variables and the Wilcoxon rank sum test for continuous variables. Values of $p < 0.05$ (two-sided test for Fisher's exact test) were considered significant.

Results

There were no significant differences in age, sex, body height, body weight, or preoperative use of beta blockers between the two groups (Table 1). Additionally, there were no significant differences in surgical procedures between the two groups (Table 1).

The occurrence of sustained AF for $>$ 1 hr was significantly lower in the amiodarone group than in the control group (30.0% vs. 63.6%, respectively; $p = 0.04$). Additionally, the total duration of AF during the one week after surgery was significantly shorter in the amiodarone group than in the control group (296.8 ± 676.9 vs. 921.4 ± 1641.6 min, respectively; $p = 0.04$). The frequency of postoperative beta blocker administration tended to be lower in the amiodarone group (30.0% vs. 59.1%, respectively; $p = 0.07$); likewise, the frequency of antiarrhythmic drug use tended to be lower in the amiodarone group (20.0%) than in the control group (50.0%, $p = 0.06$). There were no significant differences in which postoperative day the first episode of AF occurred, recurrence of AF, direct current defibrillation for AF, or anticoagulant therapy

for AF between the two groups (Tables 2, 3). However, the postoperative hospital stay was significantly shorter in the amiodarone group than in the control group (17.3 ± 6.1 vs. 24.5 ± 11.3 days, respectively; $p = 0.01$). Only one patient was discharged within two weeks after surgery in the control group, whereas seven patients were discharged within two weeks in the amiodarone group. Thus, significantly fewer patients in the amiodarone group had a hospital stay of more than two weeks compared to the control group (65.0% vs. 95.5%, respectively; $p = 0.02$). The 30-day mortality rate was 0% in both groups. There was one case of stroke in the control group (Table 4), and there was one case of bradycardia (50 bpm, postoperative day 0) in the

Table 1. Patient characteristics

	Amiodarone (n = 20)	Control (n = 22)	*p*-value
Age (years)	75.4 ± 8.1	76.6 ± 7.0	0.58
Sex (male)	13 (65.0)	10 (45.5)	0.23
Body height (cm)	157.3 ± 10.2	154.7 ± 9.5	0.31
Body weight (kg)	57.4 ± 9.2	57.3 ± 13.2	0.48
Preoperative beta blockers	6 (30.0)	12 (54.6)	0.13
Type of surgery			
・Combined valve surgery	2 (10.0)	7 (31.8)	0.14
・AVR	11 (55.0)	11 (50.0)	0.77
・OPCAB	7 (35.0)	4 (18.2)	0.30

Data are expressed as mean ± standard deviation or as the number of patients (%).
AVR: aortic valve replacement, OPCAB: off-pump coronary artery bypass.

Table 2. Atrial fibrillation (AF) study endpoints

	Amiodarone (n = 20)	Control (n = 22)	*p*-value
Occurrence of sustained AF > 1 hr	6 (30.0)	14 (63.6)	0.04
Total duration of AF over one week (min)	296.8 ± 676.9	921.4 ± 1641.6	0.04
Postoperative beta blockers	6 (30.0)	13 (59.1)	0.07
Antiarrhythmic medications for AF	4 (20.0)	11 (50.0)	0.06
DC for AF	3 (15.0)	5 (22.7)	0.70
Anticoagulant therapy for AF	1 (5.0)	4 (18.2)	0.35

Data are expressed as the number of patients (%).
DC: direct current defibrillation

Table 3. Clinical outcomes of patients with atrial fibrillation (AF)

	Amiodarone (n = 7)	Control (n = 14)	*p*-value
Time to first episode of AF (POD)	3.4 ± 1.3	2.7 ± 1.6	0.11
Recurrence of AF	3 (42.9)	12 (85.7)	0.12

Data are expressed as mean ± standard deviation or as the number of patients (%).
POD: postoperative day

amiodarone group. Amiodarone infusion caused no major side effects, such as hypotension (systolic blood pressure < 80 mmHg) or liver dysfunction (transaminase > 100 units/dl).

Discussion

There were two major findings in this study: [1] the use of amiodarone infusion for 48 hr postoperatively prevented postoperative sustained AF for more than one hr, and [2] the hospital stay period after surgery was significantly shorter in the amiodarone group.

Although previous studies have shown the effectiveness of amiodarone for the prevention of AF[10-19, 22-24], the clinical use of amiodarone lacked standardization. The American Heart Association / American College of Cardiology / Heart Rhythm Society guidelines recommend the preoperative oral use of amiodarone[9]. However, intravenous use has several advantages compared to oral administration[25] (Table 5). First, intravenous amiodarone has little effect on heart rate during sinus rhythm, and the frequency of sinus bradycardia is low. Moreover, it does not prolong the QTc duration. Second, it has minimal antithyroid action. Third, the bioavailability of oral amiodarone is approximately 35% to 65%, and the oral form requires several days until the onset of antiarrhythmic action. Conversely, the bioavailability of intravenous amiodarone is 100%, the onset of action is fast, and intravenous amiodarone can be used in the ICU immediately after surgery.

Amiodarone has been associated with multiple organ toxicity issues involving the lungs,

Table 4. Incidence of major morbidity, mortality and postoperative hospital stay

	Amiodarone (n = 20)	Control (n = 22)	*p*-value
Cerebrovascular accidents	0	1 (4.5)*	1.00
30-day mortality	0	0	
Postoperative hospital stay (days)	17.3 ± 6.1	24.5 ± 11.3	0.01
Over 2-week postoperative stay	13 (65.0)	21 (95.5)	0.02

Data are expressed as mean ± standard deviation or as the number of patients (%).
*Cerebrovascular accident was a stroke.

Table 5. The differences between oral and intravenous amiodarone*

	Oral amiodarone	Intravenous amiodarone
Slowing of phase 4 depolarisation in the sinus node	+++	+
Heart rate	↓ ↓	− / ↓
QTc duration	↑ ↑ ↑	− / ↑
Interaction with the thyroid axis (block conversion of thyroxine to triiodothyronine)	+++	−
Bioavailability	35% ~ 65%	100%
Onset of antiarrhythmic action	delay	rapid

+; yes or present, −; no or absent, ↑; increase, ↓; decrease.
*Taken from Desai AD, *et al. Ann Intern Med*. 1997 (Ref # 25).

thyroid, and liver; these side effects are related to the total amount of amiodarone exposure, i.e., dosage and treatment duration[25,26]. Therefore, the prophylactic use of amiodarone should be the lowest effective dosage possible for the shortest effective duration. Most of the side effects involving multiple organ systems are thought to be minimal with short-term intravenous therapy[25]. Additionally, studies have shown that postoperative AF occurs most frequently on postoperative day two[4,5]. Using our method, the concentration of amiodarone would be in the effective range during this period. Thus, the 48-hr use after the operation in the ICU is a safe and effective usage of intravenous amiodarone.

This study has several limitations. First, the cohort was comprised only of patients with a high risk of AF, which we have defined. A randomized trial with all open-heart surgery patients might have shown more advantages because we had very few side effects caused by our protocol. Second, the study size was rather small. The difference in the occurrence of AF ($p = 0.12$) might have reached statistical significance in a larger study; however, we believe that the effectiveness of the 48-hr use of amiodarone can be demonstrated by the reduced occurrence of sustained AF for more than 1 hr and the shorter total duration of AF during one week.

Conclusions

The prophylactic use of intravenous amiodarone infusion only during the immediate postoperative period is a safe and effective treatment to prevent postoperative AF and it shows benefits in shortening the hospital stay.

Disclosure statement

The authors have no conflicts of interest to declare.

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[Received June 20, 2019: Accepted July 11, 2019]