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Efficacy of Intraoperative Low Dose Intravenous Amiodarone in Pharmacologic Cardioversion in Patients with Preoperative Atrial Fibrillation Presenting for Mitral Valve Replacement Surgery Randomized Control Trial

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ABSTRACT

Background: Atrial fibrillation (AF) is the most common form of dysrhythmia observed in the clinical field, causing multiple morbidities, such as thromboembolic complications. Hence, the maintenance of sinus rhythm is superior to rate control. This study tests the efficacy of single- and low-dose amiodarone on the persistence of AF after surgery before transfer to the intensive care unit.

Methods: A double-blinded, randomized controlled trial assessed 113 patients who underwent mitral valve surgery with preoperative chronic AF. Patients were divided into two groups: the control group (*N* = 55) who received 50 mL of 5% dextrose over 10 min after general anesthesia induction, and the amiodarone group (*N* = 58) who received 1 mg/kg of amiodarone diluted in 50 mL of 5% dextrose over 10 min shortly after anesthesia induction.

Results: The amiodarone group had a statistically significant successful conversion of preoperative AF to normal sinus rhythm in 40 patients (72.73%). The control group demonstrated spontaneous conversion from AF to a normal sinus rhythm in seven patients (12.73%). The sinus rhythm was maintained in 60% of patients (36), as four patients reverted to AF during the hospital stay despite the initial normal sinus rhythm after the operation. In contrast, 53 (96.36%) patients in the control group were discharged from the hospital with a controlled rate of AF. In addition, low-dose amiodarone caused a statistically significant reduction in heart rates at 10, 30, and 60 min after declamping, extended throughout the first 24 h with mean heart rates of 97.233±7.311, 99.509±8.482, and 97.940±7.715 bpm, respectively. In comparison, the control group had heart rates of 115.382±7.547, 115.055±13.919, and 113.618±8.765 bpm at these times. The mean postoperative heart rate at the end of the first 24 h was 97.793±7.189 bpm in the amiodarone group and 113.036±9.737 bpm in the control group. No mortality or need for mechanical support was recorded in either group.

Conclusions: Single and low-dose intraoperative intravenous amiodarone during mitral valve surgery may be practical to aid in pharmacological cardioversion of patients with preoperative chronic AF presenting for mitral valve surgery.

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INTRODUCTION

Atrial fibrillation (AF) is the most prevalent form of dysrhythmia observed in clinical practice, resulting in multiple morbidities, including thromboembolic complications. Therefore, the maintenance of the sinus rhythm is superior to rate control not only from a hemodynamic standpoint but also in terms of postoperative symptomatic improvement [Wyndham 2000]. Moreover, AF is the irregular and rapid atrium activation in paroxysmal and chronic forms. Multiple atrial foci fire at 400 to 600 beats per minute (bpm). The atrioventricular node functions as a filter between the atria and ventricles, protecting the ventricles from rapid atrial firing [Fuster 2006]. The prevalence of AF in patients with severe mitral valve disease is 30.4% (95% CI [23.6, 37.6]), and AF is more frequent in patients with mixed mitral valve stenosis and regurgitation with a prevalence of 65.6% (95% CI [42.5, 85.4]), whereas it is 33.9% in patients with mitral stenosis (95.5% CI [28.5, 39.4]) and 21.6% in patients with mitral regurgitation (95% CI [7.8, 39.7]) [Noubiap 2020].

Surgery in less than 10% of patients with preoperative AF and mitral valve disease results in spontaneous sinus rhythm recovery in less than 10 days. According to other reports, less than 20% of patients with permanent AF who underwent surgery without AF treatment exhibited the sinus rhythm six to eight months after surgery [Rostagno 2012]. Persistent AF after mitral valve replacement is associated with worse clinical outcomes (e.g., the New York Heart Association functional class, higher transmitral gradients, and larger atria areas) [Selvaraj 2009]. Moreover, AF persistence is associated with decreased exercise tolerance, an increased risk of systemic embolism, and increased long-term mortality. Recovery of the sinus rhythm maintains the mechanical activity of the atrium and prevents tricuspid regurgitation from starting or becoming worse [Je 2008].

Among all antiarrhythmic drugs reviewed for AF, amiodarone remains the most effective, with 50% to 70% of patients achieving successful conversion and maintenance of normal sinus rhythm. Intravenous amiodarone promotes a more rapid and efficient onset of antiarrhythmic activity than oral amiodarone [Roy 2000]. Amiodarone is a class III Vaughan–Williams antiarrhythmic drug with similar effects to class I and II antiarrhythmic drugs and beta and calcium channel blocker effects [King 2022]. Therapeutic plasma levels of intravenous amiodarone range from 1.5 to 2.5 µg/mL [Goldschlager 2000]. The maximum plasma concentration and area under the curve for amiodarone was 2.9 ± 0.6 µg/mL at a dose of 1.25 mg/kg and 13.6 ± 3.4 ug/mL at 5 mg/kg, with a serum half-life of >14 days [Shiga 2011]. However, the pharmacokinetics of amiodarone is complex [Chokesuwattanaskul 2020].

In addition, amiodarone has a high protein binding capacity; however, the free drug fraction is not dependent on the total drug concentration or albumin level [Veronese 1988]. Amiodarone has a high volume of distribution (Vd) due to its relatively high hydrophobicity [Holt 1983]. Despite its high fat solubility, the amiodarone plasma concentration might fall by 25% after a few days of drug cessation, even after achieving a steady state [Pollak 2000]. The oral form of amiodarone has unpredictable bioavailability due to its slow and incomplete gastrointestinal absorption [Andreasen 1981], gastrointestinal metabolism by cytochrome P450 3A4 (CYP3A4), and excretion by P-glycoprotein [Kashima 2005].

However, amiodarone has known adverse effects, including thyroid dysfunction, hepatotoxicity, neurotoxicity, and pulmonary toxicity. Most of these adverse effects are dose- and time-dependent [Colunga Biancatelli 2019]. A meta-analysis of the harmful effects of the oral form of amiodarone has revealed that very low doses of the drug rarely cause side effects that make it necessary to stop taking it [Chokesuwattanaskul 2020].

This study evaluates the efficacy of low-dose intravenous amiodarone in converting AF to the sinus rhythm in patients undergoing mitral valve surgery.

A double-blinded, randomized controlled trial included 113 patients who underwent elective isolated mitral valve replacement with a preoperative AF rhythm >100/min as evidenced by an electrocardiogram (ECG) and an American Association of Anesthesiologists physical status of 2 to 5. Excluded patients were those who met the following exclusion criteria: refused to participate in the study; under 18 or over 60 years old; undergoing combined valve or coronary artery bypass graft surgery; with a previous PCI; on amiodarone or other rhythm modifying drugs (e.g., digoxin, beta-blockers, and CCBs); with a preoperative lung condition or oxygen saturation below 90%; with preoperative abnormal hepatic profiles identified by double the average values of ALT/AST or bilirubin or hypoalbuminemia; with preoperative renal impairment identified by a serum creatinine value of more than 1.7 mg/dL, an abnormal thyroid profile, or any history suggestive of thyroid diseases; and with diabetes because the study includes medication with 5% dextrose.

This study is registered in the Pan African Trial Registry (www.pactr.org) database ID No. (PACTR202201680255620) after obtaining the approval of the Research Ethics Committee at the Faculty of Medicine at Ain Shams University under the number code (FMASU R 218/2021/2022).

Randomization and group allocation: As described in the flow diagram, 113 patients of both sexes with chronic AF underwent mitral valve surgery. (Figure 1) Patients were recruited at the preanesthesia clinic, where they selected a closed opaque envelope from a box attached to their file retained in the clinic until the operation date. Patients were randomized into two groups. The amiodarone group (N = 58) received 1 mg/kg of amiodarone diluted in 50 mL of 5% dextrose over 10 min shortly after general anesthesia induction. The control group (N = 55) patients had the same volume of 50 mL of 5% dextrose over 10 min after general anesthesia induction.

Blinding technique: Patients randomly were assigned (at a 1:1 ratio) in a double-blinded fashion, using a computer-based program according to the patient national ID number after approval for enrollment in the study during the preoperative visit. Operating theater pharmacists (who were not involved in the study) prepared either intravenous amiodarone in a dose of 1 mg/kg diluted in 50 mL of 5% dextrose (Cardio-Mep; amiodarone hydrochloride 150 mg/3 mL) or placebo (50 mL of 5% dextrose), according to the given list. Because the solvent in the amiodarone solution is soap (polysorbate 80), shaking the bottle containing the amiodarone solution causes bubbles. Therefore, the bottles of amiodarone or the placebo were covered to ensure the blind technique.

Sample size: By using the PASS 11 program for sample size calculation with a confidence level of 90% and a margin of error of ±0.15, it is evident after reviewing the results by Selvaraj et al. (2018) [Selvaraj 2009] that the initial rhythm of AF after heart surgery was 14.3% in the amiodarone group vs. 37% in the control group. Therefore, a sample size of at least 90 patients undergoing mitral valve surgery (45 patients in each group) is sufficient to achieve the study objective.

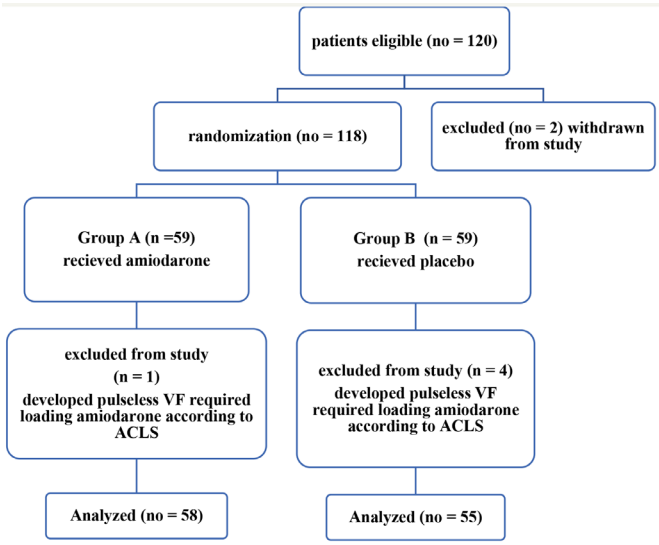

Figure 1. Consort flowchart demonstrating patient allocation

Study procedure: History, clinical examination, and routine investigations, including the complete blood count, prothrombin time, and partial thromboplastin time, were performed for all patients. In addition, a preoperative ECG (to document preoperative AF), comprehensive preoperative echocardiography (including the pathology of the mitral valve and size of the left atrium), and severity of pulmonary hypertension, if present, also were performed.

Standard monitoring was used in the operating room, including an ECG, invasive blood pressure, pulse oximetry (SpO2), temperature, and end-tidal carbon dioxide. After the standard general anesthesia induction, central venous catheter insertion, routine surgery, and cannulation of the aorta and superior vena cava just before the institution of the cardiopulmonary bypass, patients in the amiodarone group received 1 mg/kg of amiodarone diluted in 50 mL of 5% dextrose over 10 min. Patients in the control group received a placebo of 50 mL of 5% dextrose, prepared by the pharmacist and blinded for the researcher and patient.

In the case of hypotension, vasopressors were titrated as needed after stopping the infusion. This hypotension is partly due to vasodilatation and myocardial depression caused by solvents, polysorbate 80 and benzyl alcohol.

A routine bypass was conducted after heparin administration at a 4 mg/kg dose, ensuring a safe clotting time of >480 s. All patients received cold blood cardioplegia containing 30 mEq/L of KCl, 25 mEq/L of HCO3, and 100 mg of lidocaine per 1000 mL of ringer with a blood-to-cranial ratio of 4:1. A 10 mL/kg initial dose was repeated every 30 min.

Upon weaning, all patients were supported by dobutamine (5 to 10 ug/kg/min). Adding further support was performed according to the institute protocol. In patients after mitral valve surgery, we aim for a heart rate of 90 to 100 bpm. If this rate is not achieved with inotropic drugs, epicardial pacing is used.

Assessment of outcomes: After assessing the outcomes, the primary outcome was the observed persistence of AF after surgery and documented rhythm before transfer to the intensive care unit (ICU). The following outcomes were secondary: The initial repercussion rhythm was recorded shortly after declamping (whether ventricular fibrillation, normal sinus rhythm, or AF); heart rate and rhythm 10, 30, and 60 min after declamping; amount of dobutamine support necessary before transferal to the ICU and, if required, additional support; the need for epicardial pacing; the need for mechanical support, such as an intra-aortic balloon pump (IABP) or extracorporeal membrane oxygenation (ECMO); postoperative mechanical ventilation hours; mean heart rate in the first postoperative day from the monitor trend; recurrence of AF during the ICU stay; recurrence of AF or any dysrhythmia during the hospital stay; and mortality rates.

Statistical analysis: The values were presented as numbers and proportions or the mean (95% confidence interval) for normally distributed data and as the median and range for data following nonnormal distributions. The chi-square test compared the distribution of the qualitative variables in the patient groups. Quantitative variables were checked for normality using the Shapiro–Wilk test. The group means of normally distributed continuous variables were compared using the unpaired t-test. Finally, group data following nonnormal distributions were compared using the Mann–Whitney test. All tests are bilateral, and the significance level was determined at $P < 0.05$. Inferential statistics were performed using the statistical software IBM-SPSS (v. 24).

Table 1. Patient demographic data

	Control group (*N* = 55)			Amiodarone group (*N* = 58)			*P*-value
	Mean	SD	95% CI	Mean	SD	95% CI	
Age (years)	40.655	7.143	38.767-42.542	39.707	7.442	37.792-41.622	0.496
Weight (kg)	94.255	12.701	90.898-97.611	91.138	14.045	87.523-94.752	0.224
Height (cm)	172.727	4.904	171.431-174.023	172.414	3.806	171.434-173.393	0.707
BMI	31.708	4.922	30.407-33.009	30.737	5.173	29.406-32.068	0.314
Gender – male	26	47.27%	-	28	48.28%	-	0.915
Gender – female	29	52.73%	-	30	51.72%	-	0.915
Smoking	7	0.127	-	8	0.138	-	0.867
DM	6	0.109	-	7	0.121	-	0.847
HTN	5	0.091	-	5	0.086	-	0.930
COPD	4	0.073	-	4	0.069	-	0.938
NIHA	3	0.000	-	3	0.000	-	1.000
Preoperative Hb	12.189	1.011	11.922-12.456	11.913	1.096	11.631-12.195	0.172
Preoperative creatinine	0.918	0.106	0.890-0.946	0.910	0.168	0.867-0.953	0.761

Table 2. Patient data of mitral valve pathology among both groups

Dominant valve pathology	Control group (*N* = 55)		Amiodarone group (*N* = 58)		*P*-value
	No. of cases	Percent of all cases	No. of cases	Percent of all cases	
Mitral stenosis	35	63.64%	30	51.72%	
Mitral regurgitation	17	30.91%	24	41.38%	0.440
Mixed MS and MR	3	5.45%	4	6.90%	
Etiology of mitral valve pathology					
Rheumatic	45	81.82%	39	67.24%	0.076
Degenerative	10	18.18%	19	32.76%	

Table 3. Patient echocardiographic and operative data among both groups

	Control group (*N* = 55)			Amiodarone group (*N* = 58)			*P*-value
	Mean	SD	95% CI	Mean	SD	95% CI	
Mean pulmonary artery pressure (mmHg)	53.455	7.587	51.450-55.459	53.483	8.659	51.254-55.711	0.985
Right ventricular diameter (cm)	4.246	0.571	4.094-4.397	4.155	0.374	4.059-4.251	0.324
Ejection fraction (%)	58.516	4.480	57.332-59.700	58.800	2.857	58.065-59.535	0.690
Left ventricle end-diastolic diameter (cm)	5.087	0.847	4.863-5.311	5.139	0.793	4.935-5.343	0.737
Left atrial diameter (cm)	4.816	0.643	4.646-4.986	4.778	0.631	4.615-4.940	0.754
Aortic cross-clamp time (minutes)	37.200	4.240	36.079-38.321	38.517	3.642	37.580-39.455	0.081
Cardiopulmonary bypass time (minutes)	59.518	3.374	58.627-60.410	60.129	4.203	59.048-61.211	0.402
Operation time (hours)	3.969	0.225	3.910-4.028	3.898	0.314	3.817-3.979	0.177

Table 4. Patient heart rate (bpm) at different time intervals for both groups

	Control group (*N* = 55)			Amiodarone group (*N* = 58)			*P*-value
	Mean	SD	95% CI	Mean	SD	95% CI	
HR before induction	120.291	11.213	117.327-123.254	120.035	11.686	117.027-123.042	0.906
Heart rate 10 minutes after declamping	115.382	7.547	113.387-117.376	97.233	7.311	95.351-99.114	<.00001
Heart rate 30 minutes after declamping	115.055	13.919	111.376-118.733	99.509	8.482	97.326-101.691	<.00001
Heart rate 60 minutes after declamping	113.618	8.765	111.302-115.935	97.940	7.715	95.954-99.925	<.00001
Mean heart rate 24 hours postoperative	113.036	9.737	110.463-115.610	97.793	7.189	95.943-99.643	<.00001

RESULTS

Tables 1, 2, and 3 present the patient demographics, mitral valve pathology, and echocardiographic data, respectively. (Table 1) (Table 2) (Table 3) The intraoperative single- and low-dose amiodarone statistically significantly reduced heart rates at 10, 30, and 60 min after declamping. This effect extended throughout the first 24 h without a severe compromise mandating the use of epicardial pacing. (Table 4) (Figure 2). However, one patient in the control group and two in the amiodarone group required temporary pacing per the institutional protocol because patients with pulmonary hypertension require a heart rate of 90 to 100 bpm after cardiopulmonary bypass to prevent right ventricular failure. (Table 5)

Regarding the rhythm for patients after the operation, the amiodarone group had more statistically significant conversions of preoperative AF to normal sinus rhythm (40 patients; 72.73%) compared with the control group (seven patients; 12.73%; Table 5). (Figure 3) Moreover, at hospital discharge, only 36 patients (60%) in the amiodarone

Table 5. Patient postoperative rhythm and other postoperative outcomes of both groups

	Control group (N = 55)	Amiodarone group (N = 58)	P-value
Rhythm at the end of the operation			
Sinus rhythm, n (%)	7 (12.73%)	40 (72.73%)	<.001
AF rhythm, n (%)	48 (87.27%)	18 (32.73%)	
Initial repercussion rhythm after declamping			
Sinus, n (%)	5 (9.09%)	40 (72.73%)	<0.001
AF, n (%)	45 (81.82%)	14 (25.45%)	
VF, n (%)	5 (9.09%)	4 (7.27%)	
Postoperative outcomes			
Need for pacing, n (%)	1 (1.82%)	2 (3.45%)	0.59
Patients discharged from hospital with AF rhythm, n (%)	53 (96.36%)	22 (40%)	<.001
Dobutamine (ug/kg/min), median [IQR]	6 [5-8]	7 [5-10]	0.13
Mechanical ventilation (hours), mean (SD)	5.58 (1.07)	5.51 (1.12)	0.76

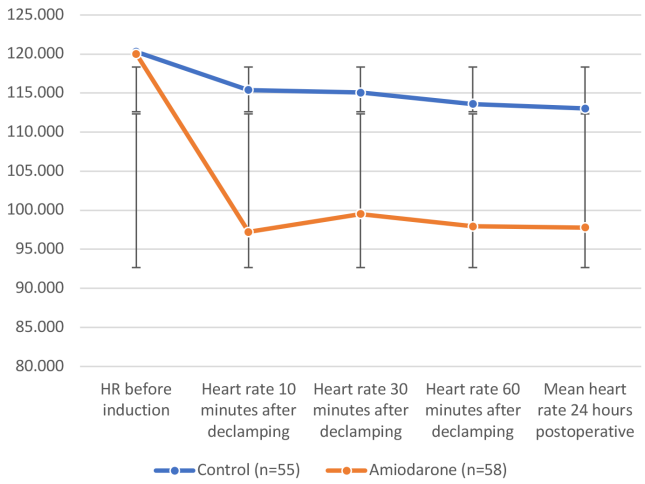

Figure 2. Patient heart rate (bpm) at different time intervals for both groups

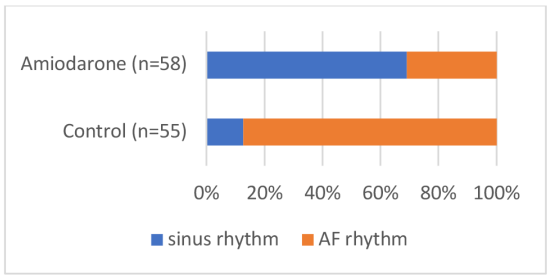

Figure 3. Patient postoperative rhythm before transfer to ICU for both groups

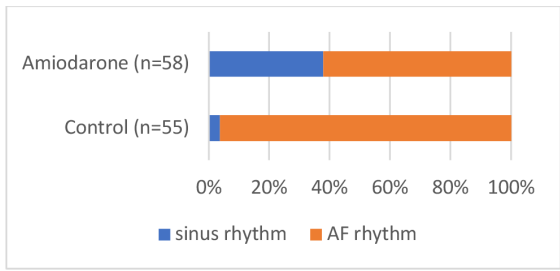

Figure 4. Patients with AF rhythm at the time of discharge from hospital for both groups

group maintained a sinus rhythm. Four patients reverted to AF during the hospital stay despite the initial normal sinus rhythm after the operation. In contrast, 53 patients (96.36%) in the control group were discharged from the hospital with a controlled AF rate. (Figure 4)

Moreover, no mortality or need for mechanical support from an IABP or ECMO was recorded in either group. Additionally, no patients developed hypotension during the drug infusion, whether receiving the placebo or amiodarone.

DISCUSSION

According to a 2018 report by the Egyptian Ministry of Health, Egypt has around 300,000 rheumatic heart disease patients [Ghamrawy 2020]. In addition, research has revealed that the prevalence of rheumatic heart disease is 31 instances per 1000 schoolchildren in Aswan, Egypt [Kotit 2017].

Focusing on the persistence of AF rhythm as an independent predictor of long-term morbidity and mortality has been extended beyond the classic complications of AF from the loss of the atrial kick and thromboembolic complications. In a subgroup analysis of 1,568 consecutive patients with AF undergoing the mitral valve procedure between 1994 and 2014, 26.0% (N = 408) had a surgical ablation of AF. Propensity-score matching was performed to compare ablated

patients with sinus rhythm versus an AF recurrence group, exhibiting significantly higher risks of moderate-to-severe TR (hazard risk, 2.427; 95% CI [1.261, 4.671]; P = .008). The AF recurrence was associated with progressive tricuspid regurgitation and significant deterioration in the right ventricle function [Wang 2016].

Recent reports have found that preoperative AF is an independent predictor of short- and long-term mortality following mitral valve surgery [Wang 2013; Lombard 2019; Ad 2018]. In addition, AF before surgery increases the long-term risks of death, thromboembolism, and tricuspid regurgitation [Wang 2013].

Amiodarone is still the classic perioperative antiarrhythmic in perioperative settings of cardiac surgery theaters despite the development of novel antiarrhythmics. However, it still has the drawbacks of not being useful for chronic AF or in the presence of structural heart disease, such as mitral valve disease [Echt 2020].

Certain antiarrhythmic medications are contraindicated in structural heart disease, defined as any situation in which the atria or ventricle size, shape, function, or structure deviates from normal (such as left ventricular hypertrophy or dilated cardiomyopathy), including coronary artery disease. Examples of such medications are flecainide [Echt 2020] and propafenone [Sarubbi 1998].

In one study, only 8.5% of patients with AF who underwent mitral valve surgery, which comprised valve repair and replacement, spontaneously reverted to a normal sinus rhythm. Immediate postoperative hemodynamic impairment is one of the potential consequences of AF. Therefore, some authors have suggested that all patients with persistent preoperative AF who undergo mitral valve surgery receive antiarrhythmic procedures or medications [Raine 2004].

Selvaraj et al. conducted a random double-blind assignment of two groups of patients, in which 42 patients intravenously received a single intraoperative dose of 3 mg/kg of amiodarone before a cardiopulmonary bypass (N = 42), and 40 patients were in the control group. In the amiodarone group, the initial repercussion rhythm after declamping was AF in 14.3% (N = 6) of the patients. The rhythm remained AF in 9.5% (N= 4) of patients until the completion of surgery. In the control group, the initial repercussion rhythm shortly after declamping was AF in 37.5% (N = 15) of patients (P = 0.035) and remained AF in 32.5% (N = 13) of patients until the conclusion of surgery (P = 0.01). At the conclusion of the first postoperative day, 21.4% of patients in the amiodarone group (N = 9) and 55% of patients in the control group (N = 22) had AF (P = 0.002) [Selvaraj 2009].

The current study suggests that intraoperative single- and low-dose amiodarone significantly reduced heart rates at 10, 30, and 60 min after declamping, which extended throughout the first 24 h with mean heart rates of 97.233±7.311, 99.509±8.482, and 97.940±7.715 bpm, respectively. In comparison, the control group had heart rates of 115.382 ±7.547, 115.055±13.919, and 113.618±8.765 bpm at these times. The mean postoperative heart rate at the end of the first 24 h of 97.793±7.189 bpm in the amiodarone group and 113.036±9.737 bpm in the control group.

Hohnloser et al. conducted a survey after providing the intervention group with a full dose of amiodarone and found a statistically significant reduction in the heart rate, which is explained by the concomitant suppression of spontaneous ectopic activity. A substantial decline in the heart rate was observed during amiodarone infusion, indicating both the sympathetic blockade and the slowing of the Phase 4 depolarization within the sinoatrial node [Hohnloser 1991].

Perioperative ablation of AF is still the subject of continuous and comprehensive research. For example, the Cox maze III procedure is considered the gold standard for surgical treatment of AF, but it is a complex surgical procedure and should still be considered, particularly in patients for whom AF ablation is of critical importance. However, due to the surgical intricacy and perception of increased morbidity, this procedure is not routinely used by cardiac surgeons [Ad 2012]. A retrospective observational study was conducted between October 2015 and June 2019 on all consecutive patients who received the maze III technique combined with valve surgery. In this study, 66 patients with persistent or long-lasting persistent AF associated with valve dysfunction underwent monopolar radiofrequency ablation. At the time of hospital discharge, 84% of these patients were free from AF [Wang 2020].

Although many studies have focused on the role of amiodarone in managing postoperative AF outside the operating room, these studies overlook its critical role inside the operating room. Therefore, further studies are needed to evaluate the effect of low-dose intravenous amiodarone during mitral valve surgery with larger cohorts of patients and more extended follow-up periods. In addition, low-dose oral amiodarone in maintaining sinus rhythm during long-term follow up should be evaluated to complement this study.

Limitations: This study was limited because the authors did not maintain amiodarone medication postoperatively. Amiodarone has been demonstrated to reduce the recurrence of AF; thus, the increased incidence of AF in this study may be attributable to the discontinuation of amiodarone during the postoperative period. The small study population further limits this study. Identifying the effect of amiodarone in patients with rheumatic AF undergoing valvular heart surgery may be aided by future trials using a larger sample and longer follow-up duration.

CONCLUSIONS

Single- and low-dose perioperative amiodarone during mitral valve surgery may be practical in aiding in the pharmacological cardioversion of patients with preoperative AF presenting for mitral valve surgery.

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