Amiodarone versus lidocaine for the prevention of reperfusion ventricular fibrillation: A randomized clinical trial

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Original Article

Abstract

BACKGROUND: Reperfusion ventricular fibrillation after aortic cross clamp is one of the important complications of open cardiac surgery and its prevention could reduce myocardial injuries. This study aimed to evaluate the efficacy of single dose of amiodarone or lidocaine by the way of pump circuit three minutes before aortic cross clamp release and compare the results with normal saline as placebo in a randomized double blinded controlled trial.

METHODS: One hundred fifty patients scheduled for first time elective coronary artery bypass graft surgery were randomly assigned to receive either single dose of amiodarone (150 mg), lidocaine (100 mg), or normal saline (5 ml) three minutes before aortic cross clamp release. The incidence of ventricular fibrillation and the need for reuse of drug were compared between these groups by chi-square, Student's t-test, Mann-Whitney test, and One-way ANOVA. SPSS software was used for statistical analysis.

RESULTS: The incidence of ventricular fibrillation is higher in the placebo group (15.9%) compare to lidocaine (11.8%) and amiodarone (8.9%) groups; however, there was no statistical difference among the three groups (P = 0.41). Moreover, the reuse of amiodarone (22.7%) was statistically higher (P < 0.05) than lidocaine (5.9%).

CONCLUSION: This study showed no difference among lidocaine, amiodarone, and placebo in preventing ventricular fibrillation after aortic cross clamp release.

Keywords: Amiodarone, Lidocaine, Ischemia Reperfusion Injury, Ventricular Fibrilation, Randomized Controlled Trial

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Introduction

Reperfusion arrhythmia is one of the important complications after pump coronary artery bypass graft (CABG) surgery. It has been shown that the incidence of postoperative supraventricular arrhythmias is 11–54% while the incidence of ventricular arrhythmias is 1.8–13%.[1] Although a large majority of such arrhythmias can be controlled by electrical cardioversions, the metabolic demands of such fibrillation or its treatment by means of direct current (DC) shock may contribute to myocardial injury.[2] Therefore, avoiding reperfusion ventricular fibrillation (RVF) after aortic cross clamp (ACC) release would reduce myocardial dysfunction during cardiopulmonary bypass (CPB).[3]

Several studies have evaluated the efficacy of amiodarone (class III antiarrhythmic agent) and lidocaine (class IB antiarrhythmic agent) in preventing postoperative RVF. Most of trials demonstrated that intravenous amiodarone is superior to other antiarrhythmics in preventing arrhythmias that may occur after coronary artery bypass operations.[4-6] However, in a recent study,

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amiodarone did not reduce the incidence of RVF compared to the placebo group while lidocaine did.[7] Therefore, the superiority of either amiodarone or lidocaine still remain a matter of controversy.

This study aimed to evaluate the efficacy of a single dose of amiodarone or lidocaine by the way of pump circuit 3 minutes before ACC release and compared the results with normal saline as placebo in a randomized, double-blinded, controlled trial.

Materials and Methods

Between September 2010 and September 2011, 150 patients scheduled for first time elective CABG were enrolled in this prospective randomized double-blinded controlled trial. On the basis of the available literature, the expected overall incidence of ventricular fibrillation (VF) after removal of the aortic cross clamp is approximately 70%. By using a chi-square test with 80% power and an alpha of 0.0167 to adjust for multiple comparisons (given the total of 3 comparisons, 0.05/3 = 0.0167 was used in the calculation), we estimated that we would need 44 patients in each group. Given the potential for patient dropouts, we planned to enroll 50 patients in each group for a total study population of 150 patients.

The protocol of this study was approved by the local ethical committee of the School of Medicine, Tehran University of Medical Sciences, Tehran, Iran (IRCT201205198860N2). A written informed consent was obtained from every patient and they were randomly assigned to three groups using balanced block randomization (block of six pieces). Exclusion criteria were any history of treatment with digoxin, amiodarone, or lidocaine (including cardiopulmonary resuscitation), contraindications to amiodarone (sick sinus syndrome, atrioventricular conduction abnormalities, thyroid disease, interstitial lung disorders, renal or liver disease, and known allergic or toxic reactions to amiodarone), combined cardiac surgery, and emergent operation.

Patients' baseline characteristics included age, sex, weight, height, body surface area (BSA), history of treatment with beta blocker, any history of MI. The patients' echocardiographic information included concomitant valve disease, left ventricular aneurysm, left ventricular ejection fraction (LVEF), and left ventricular end diastolic diameter (LVEDD).

Standard clinical protocol was used for all patients. Complete blood count, a standard coagulation profile, electrolytes, and cardiac enzyme (CPK-MB and Troponin I) were performed a day before surgery. All surgeries were performed by a single experienced surgeon at Rajaie Cardiovascular Medical and Research Center, Tehran, Iran.

All patients were monitored with pulsoxymeter, invasive blood pressure (IBP) device, central venous pressure (CVP), and electrocardiography (lead II to V5). Premedication included lorazepam, 1 mg orally the night before surgery and 1 mg one hour before surgery, plus morphine, 1 mg/kg intramuscular one hour before beginning the operation. General anesthesia was induced with sufenta 1 μg/kg, etomidate 0.2 mg/kg, and atracurium 0.5 mg/kg, and anesthesia was maintained using sufenta 1 μg/kg/hour, midazolam 1 μg/kg/min, and atracurium 4-12 μg/kg/min.

The operations were performed through a standard median sternotomy with cardiopulmonary bypass (CPB) with a flow rate of 2.4 l/m^2 and mild hypothermia at 34°C. CPB was instituted with a standard kit and a hollow-fiber membrane oxygenator (Dideco Simplex D708, Dideco). The CPB circuit was primed with Ringer's acetate and carefully de-aired. Standard cannulation consisted of arterial cannulation in the distal part of the ascending aorta and a 2-stage venous cannula inserted into the right atrium and the inferior vena cava. Myocardial preservation consisted of either anterograde or intermittent antegrade and retrograde St. Thomas solution cardioplegia. Cardioplegia was repeated every 20 to 30 minutes or on the return of electrical activity of the heart. In all the patients, the distal anastomoses were constructed first, and the proximal anastomoses were created after ACC.

Patients were randomly assigned to three groups. Group A received 150 mg (3 ml) of amiodarone diluted in 2 ml distilled water, group B received 5 ml of lidocaine 2% (100 mg), and group C (control group) received 5 ml normal saline by the way of pump circuit, 3 minutes before aortic cross clamp release.

Intraoperative variables included ACC time, CPB time, cardioplegic volume, and two samples for electrolyte and arterial blood gas (ABG) values. Patients were weaned from CPB when rewarmed to core temperature of at least 37°C and were hemodynamically stable. Electrolyte and ABG values were tested once more after weaning from CPB. Whenever the patient's rhythm was VF after ACC release, the antiarrhthmic drug was reused and the patient was treated with internal biphasic truncated exponential direct current (DC) shock with stepwise increasing energy at the frequency of 10, 10, and 20 J.

Furthermore, in spite of normal ABG and serum level of electrolytes, if this did not lead to a stable rhythm, a 30-J shock was given after the administration of another dose of antiarrhthmic drug. Reuse of antiarrythmic drug means another single dose of lidocaine in group A, amiodarone in group B, and lidocaine in group C. It should be mentioned that surgeons were blinded to the type of drugs during this study.

The primary outcome was incidence of VF requiring defibrillation during 30 minutes after ACC release. The secondary outcomes of this study were incidence of VF afterIntensive care unit(ICU) and ward admission, and reuse of antiarrhythmic drug after ACC release. The electrolyte, ABG, CPK-MB, and troponin I values were also evaluated three times (1, 6, and 24 hours) after entering the ICU in order to compare hemodynamic status of patients.

Statistical analysis

Continuous variables are summarized as mean ± SD and categorical variables are expressed as proportion (%). Univariate analyses were performed by chi-square, student's t-test, Mann-Whitney test and One-way ANOVA (where appropriate). SPSS for Windows (version 17; SPSS Inc., Chicago, IL., USA) was used for statistical analysis. Results were considered significant if P values were less than 0.05.

Results

One hundred fifty patients were randomized into three groups. Group A (n = 50) received amiodarone, group B (n = 50) lidocaine, and group C (n = 50) received placebo (normal saline) (Figure 1). The mean age for all patients was 58.69 ± 12.48. The patients' characteristics, and perioperative and postoperative variables were reported in table 1, table 2, and table 3, respectively. It has been shown that there was no statistically significant difference between the three groups in terms of patients' characteristics, preoperative data, and postoperative findings (serum electrolyte and cardiac biomarkers, medications,myocardial infarction (MI) history, left ventricular end diastolic volume, concomitant valve disease, left ventricular aneurysm, and operation condition). The detailed characteristics of outcomes such as incidence of VF and the rate of DC shock during post ACC, ICU, and ward stay, reuse of drugs after removal of ACC, and need for antiarrhythmic drugs during ICU stay are demonstrated in table 4.

One patient in the amiodarone group and another one in the placebo group demonstrated postoperative myocardial infarction.[8] The patients' rhythm and need for defibrillation were monitored at three time points including after removal of ACC, and after admission to ICU and ward. Table 5 demonstrates the results. Although the incidence of VF and the need for defibrillation was higher in the placebo group compared to the two other groups and it was higher in the lidocaine group compared to the amiodarone group, these differences did not achieve statistical significance.

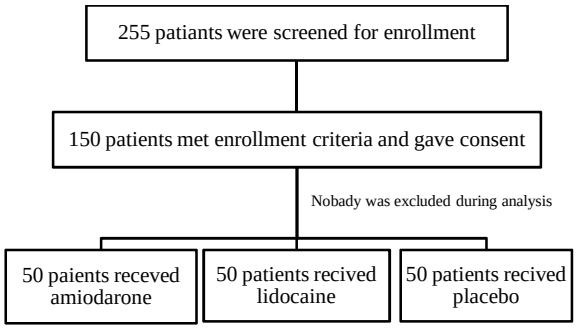

Figure1. Flow diagram of patient enrollment

Table 1. Demographic characteristics of patients

	Total (%)	Group A (%)	Group B (%)	Group C (%)	P
Sex					
Male	122 (81.40)	39 (78.40)	40 (80.0)	43 (86.40)	0.585
Female	28 (18.60)	11 (21.60)	10 (20.0)	7 (13.60)	
MI history	44 (29.30)	18 (23.50)	12 (22.7)	22 (43.20)	0.055
Beta blocker					
Propranolol	23 (15.00)	8 (15.70)	6 (11.10)	9 (18.20)	0.629
Metoral	115 (76.40)	39 (78.40)	38 (75.60)	38 (75.00)	
Carvedilol	13 (8.60)	3 (5.90)	7 (13.30)	3 (6.80)	
LV aneurysm	0	0	0	0	-
Cardioplegia					
Antrograde	91 (60.40)	28 (56.90)	32 (63.60)	31 (61.40)	0.788
Antrograde + retrograde	59 (39.60)	22 (43.10)	18 (36.40)	19 (38.60)	
Re-exploration after operation	0	0	0	0	-

MI: Myocardial infarction; LV: Left ventricular

Table 2. Preoperative continuous characteristics of patients

	Total	Group A	Group B	Group C	P
Age	58.69 ± 12.47	58.06 ± 10.47	60.64 ± 15.62	57.43 ± 10.97	0.43
Weight	72.34 ± 13.02	70.71 ± 10.72	75.38 ± 16.06	71.14 ± 11.64	0.16
Height	164.07 ± 17.80	162.29 ± 23.77	164.36 ± 16.32	165.84 ± 9.35	0.62
BSA	1.82 ± 0.25	1.83 ± 0.25	1.82 ± 0.32	1.88 ± 0.29	0.35
CPK-MB	27.68 ± 9.53	25.54 ± 7.24	24.50 ± 7.39	30.47 ± 11.53	0.21
Na	140.59 ± 3.26	140.78 ± 3.24	140.64 ± 3.27	140.32 ± 3.36	0.78
K	4.15 ± 0.44	4.10 ± 0.44	4.11 ± 0.42	4.24 ± 0.47	0.24
Ca	7.98 ± 1.54	7.98 ± 1.72	7.76 ± 1.52	8.21 ± 1.33	0.39
Mg	2.43 ± 0.40	2.50 ± 0.40	2.36 ± 0.37	2.42 ± 0.44	0.24
Cr	1.19 ± 0.23	1.16 ± 0.22	1.22 ± 0.24	1.18 ± 0.23	0.41
EF	43.24 ± 6.99	42.65 ± 6.80	43.64 ± 6.93	43.52 ± 7.36	0.75
LVEDD	4.64 ± 0.71	4.78 ± 0.77	4.61 ± 0.70	4.49 ± 0.64	0.14

BSA: Body Surface Area; CPK-MB: Creatinin Phosphokinase–MB; EF: Ejection fraction; LVEDD: Left ventricular end diastolic diameter

Table 3. Continuous intra-operative characteristics of patients

		Total	Group A	Group B	Group C	P
Cross Clamp (min)		36.34 ± 15.89	38.20 ± 19.63	35.64 ± 12.62	34.89 ± 13.98	0.56
CPB time (min)		70.14 ± 27.10	72.80 ± 29.16	72.09 ± 21.24	65.11 ± 29.67	0.33
Cardio. Volume		904.60 ± 424.18	913.53 ± 421.11	931.82 ± 419.45	867.05 ± 439.34	0.76
†	Na	135.86 ± 5.37	136.43 ± 5.83	135.13 ± 4.93	135.93 ± 5.28	0.49
	K	4.54 ± 0.52	4.67 ± 0.50	4.48 ± 0.53	4.46 ± 0.52	0.09
	pH	7.35 ± 0.66	7.35 ± 0.07	7.34 ± 0.06	7.36 ± 0.06	0.62
	HCO_3	18.35 ± 2.04	18.29 ± 2.06	18.51 ± 1.98	18.25 ± 2.11	0.81
‡	Na	135.69 ± 5.11	136.06 ± 5.25	135.31 ± 4.91	135.64 ± 5.25	0.77
	K	4.55 ± 0.59	4.54 ± 0.60	4.49 ± 0.48	4.61 ± 0.69	0.65
	pH	7.348 ± 0.07	7.35 ± 0.07	7.34 ± 0.06	7.35 ± 0.07	0.43
	HCO_3	18.54 ± 2.03	18.39 ± 2.00	18.64 ± 2.13	18.59 ± 2.00	0.81
$	Na	136.74 ± 5.54	137.47 ± 5.60	136.96 ± 5.46	135.68 ± 5.51	0.28
	K	4.52 ± 0.61	4.46 ± 0.59	4.59 ± 0.62	4.51 ± 0.62	0.58
	pH	7.36 ± 0.07	7.36 ± 0.07	7.36 ± 0.07	7.34 ± 0.07	0.60
	HCO_3	18.74 ± 2.18	18.24 ± 2.20	19.00 ± 1.99	19.07 ± 2.29	0.11

† The first laboratory test during cardiopulmonary bypass machine; ‡ The last laboratory test before weaning from CPB
$ The first laboratory test after weaning from CPB; CPB: cardiopulmonary bypass; Cardio. Volume: Cardioplegic volume

Reuse of drug means using another single dose of lidocaine in group A, another single dose of amiodarone in group B, and a single dose of lidocaine in the placebo group after removal of aortic cross clamp. Table 5 shows that the reuse of drug incidence was statistically higher in the amiodarone group than the lidocaine group.

Discussion

Reperfusion after myocardial ischemia induces ventricular arrhythmias such as ventricular tachycardia and ventricular fibrillation.[9-10] Reperfusion ventricular fibrillation is considered to be caused by a re-entry resulting from decreased conduction velocity and increased inhomogeneity in the refractory periods of cardiomyocytes.[11]

It has been shown that agents that have sodium channel blockade are capable of preventing reperfusion-induced arrhythmias.[12] Lidocaine, a class IB antiarrhythmic drug, binds to sodium channels, decreases the slope of phase 4 depolarization, and increases the diastolic electric current threshold in Purkinje fibers. Rinne and Kaukinen studied the effect of an intravenous bolus of lidocaine given before clamping the aorta followed by a continuous infusion for 20 hours.[13] They reported neither an increase in cardiac protection nor a decrease in the incidence of RVF. Baraka et al. showed that the administration of a bolus of 100 mg of lidocaine by the way of the pump 2 min before releasing the ACC can significantly decrease the incidence of RVF, without increasing the incidence of atrioventricular block.[14] In our study, a single dose of 100 mg

Table 4. Postoperative laboratory results duringintensive care unit (ICU) stay

		Total	Group A	Group B	Group C	P
†	Na ICU	136.31 ± 5.18	135.43 ± 4.77	136.82 ± 5.55	136.82 ± 5.24	0.31
	K ICU	4.533 ± 0.64	4.61 ± 0.70	4.40 ± 0.57	4.58 ± 0.62	0.24
	Mg ICU	2.439 ± 0.39	2.40 ± 0.39	2.43 ± 0.45	2.49 ± 0.34	0.50
	Ca ICU	8.03 ± 1.45	8.09 ± 1.20	8.25 ± 1.26	7.75 ± 1.82	0.25
	pH ICU	7.317 ± 0.36	7.29 ± 0.42	7.37 ± 0.07	7.30 ± 0.45	0.52
	HCO_3 ICU	18.46 ± 2.09	18.43 ± 2.08	18.33 ± 2.04	18.64 ± 2.17	0.78
	CPK MB ICU 1	57.09 ± 34.81	57.22 ± 28.84	54.91 ± 30.51	59.18 ± 44.57	0.84
‡	Na ICU	136.93 ± 5.68	136.71 ± 6.22	137.24 ± 5.23	136.86 ± 5.58	0.89
	K ICU	4.47 ± 0.58	4.42 ± 0.59	4.45 ± 0.45	4.55 ± 0.68	0.54
	pH ICU	7.36 ± 0.07	7.36 ± 0.07	7.36 ± 0.067	7.35 ± 0.06	0.88
	HCO_3 ICU	18.46 ± 2.09	18.33 ± 2.15	18.78 ± 2.11	18.28 ± 2.02	0.46
	CPK MB ICU	53.31 ± 29.03	57.27 ± 31.14	46.09 ± 23.12	55.93 ± 31.03	0.61
	Troponin ICU	1.25 ± 0.89	1.34 ± 1.05	1.23 ± 0.75	1.14 ± 0.80	0.52
*	Na ICU	136.83 ± 5.79	136.65 ± 5.72	137.67 ± 6.13	136.18 ± 5.52	0.66
	K ICU	4.54 ± 0.60	4.51 ± 0.53	4.61 ± 0.65	4.49 ± 0.62	0.61
	Ca ICU	8.30 ± 0.84	8.25 ± 0.89	8.39 ± 0.82	8.28 ± 0.79	0.66
	CPK Mb ICU	58.41± 34.71	55.51 ± 28.71	64.98 ± 44.86	55.20 ± 28.84	0.31
	Cr ICU	1.21 ± 0.25	1.19 ± 0.26	1.24 ± 0.28	1.21 ± 0.20	0.65
	Postoperative LVEF	44.64 ± 6.75	45.00 ± 7.14	44.89 ± 6.96	43.98 ± 6.15	0.73

† The first test at ICU; ‡Six hours after admitting to the ICU; * Twenty four hours after admitting to the ICU
CPK Mb: Creatinin Phosphokinase–Mb; ICU: Intensive care unit; LVEF: Left ventricular ejection fraction

Table 5. Final results for the three groups

	Group A (%)	Group B (%)	Group C (%)	P
VF after removal of ACC	6 (11.8)	5 (8.9)	8 (15.9)	0.562
VF during ICU stay	0	1 (2.3)	0	0.595
VF during ward stay	0	0	0	-
Defibrillation after removal of ACC	6 (11.8)	4 (6.8)	8 (15.9)	0.410
Defibrillation during ICU stay	0	0	0	-
Defibrillation during ward stay	0	0	0	-
Reuse of drug	3 (5.9)	11 (22.7)	-	0.048

VF:Ventricular fibrillation; ACC: Aorticcross clamp; ICU: Intensive care unit

lidocaine was administered 3 minutes before removal of ACC. The results did not show any statistical difference between the lidocaine group and the placebo group for incidence of ventricular fibrillation (0.56).

Amiodarone [2-butyl, 3-(4-diethylaminoethoxy, 3, 5-diiodo, benzoyl) benzofuran hydrochloride] is a class III antiarrhythmic agent which displays a wide cellular electrophysiologic spectrum, inhibiting the potassium currents, sodium currents, and L-type calcium currents in isolated cardiomyocytes.[15,16] Animal studies confirmed that amiodarone use not only improved the cardiac metabolic efficiency after ischemic reperfusion period but also decreased the transmural dispersion of repolarization of the heart, which is closely associated with the development of ventricular arrhythmias.[17-20] Bigdelian and Gharipour demonstrated that postoperative course of amiodarone administration is an effective, possibly safe, well-tolerated, and widely applicable therapy for the prevention of postoperative atrial tachyarrhythmia after cardiac surgery.[21] In our study, 150 mg amiodarone was administered 3 minutes before removal of aortic cross clamp. Although amiodarone could reduce the incidence of VF from 15.9% to 11.8%, it was not statistically significant (P = 0.18). Ayoub et al. demonstrated that although amiodarone could not reduce the frequency of VF compared to the control group, it did reduce the requirements of direct current shocks energy in the amiodarone group (16.7 J) as compared to the control group (25.8 J).[7] In contrast, Samantaray et al. showed that amiodarone administration could reduce the incidence of VF. However, they considered only 17 patients in each group which was significantly lower than our study and the difference in the results might be related to this fact.[22]

Furthermore, the results showed that the incidence of VF was lower in the amiodarone group

(8.9%) than the lidocaine group (11.8%) which was not statistically significant (0.41). This is not in agreement with the results of Ayoub et al. in which the incidence of VF in the lidocaine group was significantly lower than both amiodarone and control groups.[7] Recently, Mauermann et al. reported that neither amiodarone nor lidocaine reduced the incidence of ventricular fibrillation in patients undergoing a variety of cardiac surgical procedures.[23] However, amiodarone decreased the number of shocks required to terminate ventricular fibrillation. These results were compatible with the results of our study.

Many factors might contribute to the incidence of VF such as preoperative and intraoperative acidosis, hypoxia, and potassium level. In this study we evaluated these metabolic abnormalities for all three groups before cross clamp, two times during CPB, after removal of ACC, and three times during ICU stay. Moreover, any history of MI, concomitant valve disease, use of beta blocker, type of cardioplegia, and aortic cross clamp time might influence the incidence of VF. In our study there was no statistical difference in these predisposing factors among the three groups. Therefore, the incidence of RVF could be attributed to the administration of amiodarone, lidocaine, and placebo, respectively.

The current trial has some limitations. First, the mean left ventricular ejection fraction was normal. Thus, it is unclear whether our results are applicable to patients with decreased left ventricular function. Second, the dose of administered amiodarone may not have been high enough to achieve therapeutic tissue levels given the added circulatory volume of the CPB circuit.

Conclusion

In conclusion, the present study demonstrated lower incidence of VF after ACC release in amiodarone and lidocaine groups compared to the placebo group and in amiodarone group compared to lidocaine group; these results did not achieve statistical significance (P = 0.41).

Conflict of Interests

Authors have no conflict of interests.

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