Original Article

Indian Journal of Anaesthesia and Analgesia
2017, 4 (3, Part-I), 569-574
DOI: http://dx.doi.org/10.21088/ijaa.2349.8471.4317.2

A Comparative Study of Intraoperative Use of Amiodarone Verses Diltiazem in Patients with Rheumatic Valvular Heart Disease and Atrial Fibrillation Undergoing Valve Replacement Surgery

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Abstract

Background and aim: The studies on effects of amiodarone and diltiazem, on conversion of atrial fibrillation (AF) to normal sinus rhythm (NSR) in patients of rheumatic heart disease (RHD) with AF undergoing valve replacement surgery are very less. In this study, we compared the effect of amiodarone and diltiazem on conversion of AF to NSR. *Methods:* Seventy five patients of RHD with chronic AF undergoing valve replacement surgery were randomly assigned into three groups(each contained 25 patients). In group C normal saline was given. In group A, injection amiodarone 3mg/kg, IV given over 10 minute before skin incision followed by continuous infusion at 0.3mg/kg/h till the end of surgery. In group D injection diltiazem 0.25mg/kg, IV over 10 minute followed by continuous infusion at 0.1mg/kg/h till the end of surgery. *Results:* The percentage of patients converted to NSR at aortic declamping was not significantly different in amiodarone and diltiazem group: 80% in amiodarone and 92% in diltiazem group. The conversion to NSR in control group was 28% and the difference was significant when compared to amiodarone (p=0.00) and diltiazem (p=0.00) group. The patients required DC shock in diltiazem group (4%) were significantly less as compare to amiodarone (28%, p=0.02) and control (44%, p=0.00) group. *Conclusion:* Amiodarone and diltiazem both are equally effective and safe to convert AF to SR. Diltiazem is better than amiodarone to reduce the requirement of defibrillation.

Keywords: Amiodarone; Diltiazem; Atrial Fibrillation; Rheumatic Heart Disease.

Introduction

Atrial fibrillation (AF) is most common and sustained arrhythmia seen in clinical practice [1]. In developing countries rheumatic heart disease (RHD) is most common underlying condition in patients with AF. AF is associated with incidence of thromboembolic events in 17-18% of patients. In one study it is observed that maintenance of normal sinus rhythm (NSR) in patients of AF leads to symptomatic improvement [2]. Maintenance of NSR is superior to rate control in patients with rheumatic AF in respect of effect on exercise capacity, quality of life, morbidity and mortality [3].

According to guidelines from American College of Cardiology (ACC), American Heart Association (AHA) and European Society of Cardiology (ESC), the initial strategy to manage patients with AF includes anticoagulation, as well as rate control [4]. For chronic AF, rhythm control is needed when rate control is not adequate to control symptoms. Diltiazem, a calcium channel blocker, shows significant decrease in incidence of AF [5]. Amiodarone has shown the most promising results with successful conversion and maintenance of NSR achieved in 50%-70% of patients [6]. There is lack of reports regarding the intraoperative use of intravenous amiodarone and diltiazem in patients with AF of rheumatic origin, undergoing valvular heart surgry. In this study we compared the effect of intravenous amiodarone and diltiazem on conversion

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Received on 15.04.2017, **Accepted on** 09.05.2017

of AF into NSR in patients of RHD undergoing valvular heart surgery.

Methods

This study was framed in prospective double blind case control manner. The study was started after receiving approval from institutional ethical committee. The patients with RHD and undergoing elective valve replacement surgery under cardiopulmonary bypass were screened for participation. The patients with RHD who were NYHA class II or III and having chronic AF (>1Yr) were included in this study. Pregnancy, resting heart rate <50/min, uncontrolled heart failure, sick sinus syndrome, atrio-ventricular block, serum creatinine >2mg/dl, patients on cimetidine, phenytoin, cholestyramine and cyclosporine therapy, patients who were allergic to amiodarone or had received amiodarone therapy in past four month, patients with thyroid disease, high value of aspartate and alanine amino transferase (concentration >4 times the upper limit) were exclusion criteria.

After applying exclusion and inclusion criteria, 75 patients selected for the study. These patients were randomly grouped in a double blind manner in 3 groups, group C (Control), group A (Amiodarone), and group D (Diltiazem). Each group contains 25 patients. All the patients obtained the morning dose of beta blockers. Digoxin and calcium channel blockers was omitted on day of surgery. All the patients were premedicated with intramuscular injection of morphine 0.1 mg/kg and promethazine 0.5 mg/kg, 45 min before surgery. Preanaesthetic check-up and NBM status were checked. In the operation theatre patient's identification were ensured. ECG, pulse oximeter and NIBP attached to obtain baseline parameters. IV line secured. Arterial line and internal jugular venous cannulation was established.

All the patients were induced with IV midazolam 0.05 mg/kg, IV fentanyl 10 mcg/kg and IV rocuronium 0.9 mg/kg with simultaneous oxygenation with 100% oxygen. Patients were intubated with appropriate size endotracheal tube. Anaesthesia was maintained with incremental doses of fentanyl, midazolam, vecuronium. IV ceftazidime 1g were given to all patients as a part of institutional protocol.

In group C, normal saline 50 ml was given within 10 minutes before skin incision followed by continuous IV infusion till the end of surgery. In group A, injection amioderone 3 mg/kg diluted in 50 ml normal saline, was given within 10 minutes before skin incision followed by infusion at the rate of 0.3mg/kg/h till the end of surgery. In group D, injection diltiazem 0.25 mg/kg diluted in 50 ml normal saline, given with in 10 min before skin incision followed by infusion at the rate of 0.1 mg/kg/h till the end of surgery. All the study drugs were given through central venous line. The drugs or saline was prepared and administered in a random (sealed envelope technique) manner by one of my colleague who was not involved in patient care. The anaesthesiologist involved in patient care in operating room or ICU was blinded to the patient group. Intraoperative vitals (HR, SBP, DBP, MAP, SPO2 and Rhythm) were noted just before bolus infusion, 5 min after bolus infusion and then every 15 min interval till just before cardiopulmonary bypass (CPB) and every 15 min. after aortic cross clamp (ACC) release. During bradycardia (HR less than 60 beat/min) or hypotension (SBP less than 90 mmHg) drugs infusion was temporarily discontinued. Preload was optimised to achieve central venous pressure (CVP) of 10 mmHg. Inotropes infusion was started to treat persistent hypotension despite preload optimisation. Drugs infusion was restarted after achieving haemodynamic stability. Pre-CPB conversion of AF to NSR, if any, was observed.

Heparin 4 mg/kg was given IV to achieve adequate anticoagulation-activated clotting time of 480 second. The valve replacement surgery was performed under CPB with mild hypothermia using standard extracorporeal techniques. CPB circuit was primed with lactated Ringer's solution and/or packed red blood cells to achieve haematocrit of more than 24% on CPB. As per the institutional protocol, nitroglycerine infusion 0.5 μg/kg/min was started at the onset of CPB to achieve adequate rewarming. All the patients were rewarmed to 36.C. Serum potassium levels were optimised to 4-4.5 mEq/l by adding incremental doses (5mEq) of potassium chloride to the venous reservoir in extracorporeal circuit. An incremental dose of magnesium sulphate starting from 10 mg/kg was added to CPB circuit if hypomagnesaemia was detected.

Initial rhythm after the release of ACC was noted. If it was AF, cardioversion was attempted with internal paddles with stepwise increasing energy [10 J, 20 J, 30 J biphasic]. If HR was less than 60/min, atrial pacing (epicardial) initiated. If the patient had ventricular fibrillation (VF) or ventricular tachycardia (VT), this was also treated with internal defibrillation with stepwise increasing energy. If the patient had atrioventricular block A-V sequential pacing (epicardial) was initiated.

Dobutamine was started for inotropic support if hypotension was encountered. Adrenaline was added as a second introtopic agent to treat persistent hypotension despite 10 µg/kg/min of dobutamine infusion. Aorta was decannulated after reversal of residual action of heparin by administration of protamine sulphate (6 mg/kg) intravenously. After surgical closure, the patient was transferred to the post operative ICU. A 5lead ECG was continuously monitored. Post-operative vitals (HR, SBP, DBP, MAP, rhythm, SPO2) were noted at 1h, 4h, 12h and 24h.

The following were primary outcome parameters: AF at release of aortic cross clamping, number of shocks and response to cardioversion/ defibrillation, amount of energy needed for cardioversion, the recurrence of AF at the end of surgical procedure, in the first 24 hours of post operative period. The sample size was calculated 15 subjects in each three groups at á error 0.05 and power 80% assuming difference in means of amount of energy needed for electro-cardioversion, that was 18.03±16.5. All the data were entered on Excel Sheet M.S. Office Excel-2007 and analyzed statistically using SPSSs Statistical software (ver.18.0.0) and XL-stat. All the quantitative data were summarized in the form of Mean±SD. The difference between mean value of three groups was analyzed using ANOVA one way test and within groups using paired T-test. All the qualitative data were summarized in the form of proportions. The difference between proportions was analyzed using Chi square test. The levels of significance and –α error were kept 95% and 5% respectively, for all statistical analysis. P values <0.05 were considered as Significant (S) and P value > 0.05 as statistically, Non Significant (NS).

Results

No difference was seen in the patient's characteristics and demographic data among the three groups (Table 1). The intra-operative data of three groups is summarised in Table 2. The primary outcome data of three groups are summarised in Table 3. The heart rate and mean arterial pressure (MAP) at different time interval are depicted in Graph 1 and Graph 2 respectively. There was no significant difference seen in the mean basal heart rate and mean MAP.

The mean heart rate at 5 min after bolus infusion, in amiodarone group (84.8±18.4) and diltiazem group (88.1±17.4) was significantly low (p=0.01) in compare to control group (100.5±18.4). At other observation time point no significant difference were seen in intra-operative mean heart rate between three groups. The intra-operative MAP at 5 min after bolus infusion was significantly low (p=0.03) in amiodarone group (83.4±6.3) and diltiazem group (79.4±10.3) in comparison to control group (85.8±8.2). At other observation time point no significant difference was seen in intra-operative mean arterial pressure. At release of ACC, NSR was observed in 7(28%), 20(80%) and 23(92%) patients in group C, group A and group D respectively. AF was observed in 13(52%), 2(8%) and 2(8%) patients in group C, group A and group D respectively. The difference was significant (p=0.00) among three group. On comparison between amiodarone and diltiazem group, no significant difference (p=0.66) was seen. At the end of the surgery, AF was observed in 13(52%), 4(16%) and 4(16%) patients in group C, group A and group D respectively. The difference was significant (p=0.01) among three groups. On comparison between amiodarone and diltiazem group, no significant difference (p=0.35) was seen.

At 24 h after surgery, AF was seen in 17(68%), 6(24%) and 5(20%) patients in group C, group A and group D respectively. The difference was significant (p=0.0005) among three groups. However, when amiodarone and diltiazem groups were compared, no significant difference (p=0.733) was observed. Five patients (20%) in control group, 5 patients (20%) in amiodarone group and 0 patients in diltiazem group required anti-arrhythmic agents for VF/VT. The difference was significant between group A and D (p=0.02). Among three groups comparison, the difference was insignificant.

Four patients (16%) in group C, 10 patients (40%) in group A and 7 patients (28%) in group D required inotropes during bolus infusion. However the difference was not significant among three groups (p=0.17). Three patients (12%) in group A and one patient in each group D & C required temporary pacing during surgery. No significant difference was seen among 3 groups in respect of requirement of temporary pacing (p=0.42). Eleven patients (44%) in group C, 7(28%) patients in group A and 1(4%) patient in group D required DC shock. The requirement of DC shock was significantly less in diltiazem group in compared to amiodarone group (p=0.02) and also in compared to control group (p=0.00).The required mean energy of DC shock was 13± 18.4 J in control group, 5±9 J in amiodarone group and 1.2±6 J in diltiazem group. The required energy was significantly less in diltiazem group in compared to control group (p=0.005). Between amiodarone and diltiazem group no significant difference was seen in respect of required energy for DC shock (p=0.94).

Table 1: Patient Characteristics[mean ± SD]

Patient Characteristics	Group C n=25	Group A n=25	Group D n=25	P value for overall comparison
Age (in years)	36.4±11.6	40.7±10.7	36.9±11.3	0.337
Body Weight(in kg)	48.2±10.3	48±8.3	48.9±9.4	0.936
Male :Female	13:12	11:14	9:16	0.522
Height (in cm)	168.2±6.5	164.3±7.9	165.6±6.2	0.130
NYHA Class				
Class II	5	3	5	0.690
Class III	20	22	20	
LVEF	57.4±3.9	56.4±4.3	56.3±7	0.721
Type of heart surgery				
MVR	18	20	18	
AVR	1	1	2	0.903
DVR	6	4	5	
Pre operative LA size(in mm)	53.6±12	53.1±13	51±8.5	0.694
Severity				
Moderate	0	1	0	0.363
Severe	25	24	25	

SD = standard deviation; LA = left atrium, NYHA = New York Heart Association functional classification, MVR = mitral valve replacement, DVR = double valve replacement, AVR = aortic valve replacement

Table 2: Intraoperative Events [mean ± SD]

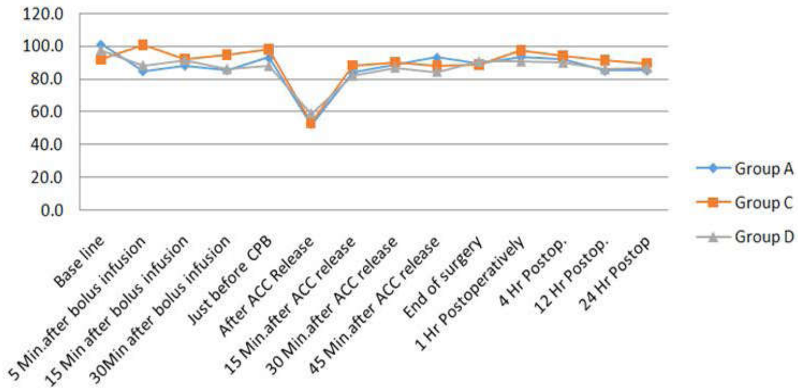
Intraoperative Events	Group A n=25	Group C n=25	Group D n=25	P value for overall comparison	P value for Group A&C	P value for Group C&D	P value for Group A &D
CPB time(min)	70±15	71.6±19.5	66.2±22.3	0.600	0.747	0.371	0.488
ACC time (min)	51.4±12.2	49.3±13.1	46.5±16.1	0.452	0.556	0.225	0.497
Basal HR(/min)	101.1±25.7	91.6±12.8	97.4±20	0.250	0.106	0.228	0.571
HR-5 min after drug infusion(bolus)	84.8±18.4	100.5±18.4	88.1±17.4	0.008	0.004	0.018	0.516
Difference in HR (/min)	-16.3±13.5	8.4±18.1	-9.3±14.6	0.000	0.000	0.000	0.085
Basal MAP	91.9±6.4	87.6±7.5	86.0±8.4	0.066	0.093	0.500	0.025
MAP-5 min after drug infusion(bolus)	83.4±6.3	85.8±8.2	79.4±10.3	0.030	0.245	0.019	0.106
Difference in MAP	-8.2±7.1	-1.8±11.1	-6.8±7.1	0.027	0.020	0.371	0.488
Use of anti- arrhythmic agent for VT/VF	5(20%)	5(20%)	5(20%)	0	0.056	1	0.018
Use of inotropes during bolus infusion	10(40%)	4(16%)	7(28%)	0.168	0.059	0.306	0.370

SD = standard deviation; P < 0.05 = statistically significant; CPB = cardio pulmonary bypass; ACC = aortic cross-clamp time; HR = heart rate; VT/VF = ventricular tachycardia/ventricular fibrillation; MAP = mean arterial pressure.

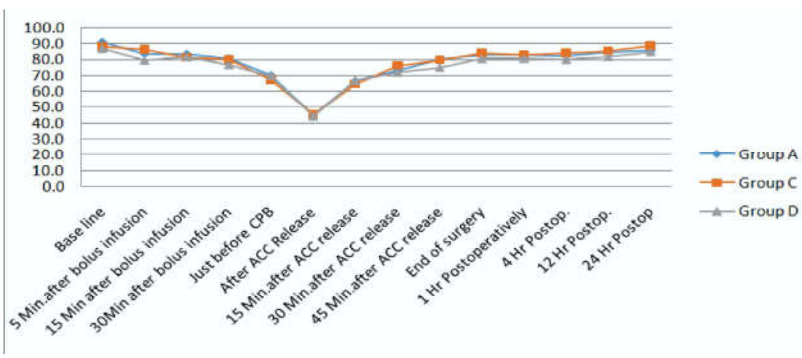
Table 3: Primary out come

Primary outcome	Group C	Group A	Group D	P value for overall comparision	P value for Group A&C	P value for Group C&D	P value for Group D &A
Rhythm after ACC release							
SR	7(28%)	20(80%)	23(92%)				
AF	13(52%)	2(8%)	2(8%)	0.0001	0.002	0.001	0.659
VF	5(20%)	2(8%)	0(0%)				
ASYSTOLE	0(0%)	1(4%)	0(0%)				
Response to cardioversion successful/ total attempt of cardioversion	6/11	5/7	0/1	0.377	0.305	0.500	0.375
No. of attempts of cardioversion needed	0.8±1.1	0.4±0.7	0.1±0.4	0.004	0.932	0.002	0.056
Amount of energy needed for cardioversion (joules)	13±18.4	5±9.4	1.2±6	0.004	0.060	0.005	0.094
AF at the end of surgery(No. of patients)	13(52%)	4(16%)	4(16%)	0.011	0.027	0.012	0.350
Need for temporary pacing(no. of patients)	1(4%)	3(12%)	1(4%)	0.424	0.297	1	0.297
Need for DC shock(no. of patients)	11(44%)	7(28%)	1(4%)	0.005	0.239	0.001	0.021
No. of patients with AF at 24 hr after surgery	17(68%)	6(24%)	5(20%)	0.0005	0.0018	0.0006	0.733

P < 0.05 = statistically significant; ± = values represent mean ± standard deviation; AF = atrial fibrillation



Graph 1:



Graph 2:

Discussion

AF is a most common and sustained cardiac arrhythmia observed in clinical practice [1]. It causes significant haemodynamic instability in patients having RHD. Restoration of NSR is beneficial in terms of relief of symptoms, improvement in exercise capacity, quality of life, decrease in stroke incidences and thus improvement in survival [3]. In one study, only 8.5% patients restored NSR following valve replacement and valve repair surgery [6]. The rationale behind the use of anti-arrhythmic procedure or drugs is to prevent haemodynamic instability during immediate post-operative period [6].

Amiodarone are being used as anti-arrhythmic drug since 1970. High lipid solubility provides it long half life. It has a wide anti-arrhythmic profile and IV amiodarone has a faster onset of action than oral amiodarone. IV amiodarone reduces incidences of sudden death after myocardial infarction [7,8]. On the other hand, diltiazem is a calcium channel blocker known to be effective in the treatment of angina pectoris, hypertension, and supraventricular arrhythmias [9].

In the stroke prevention in atrial fibrillation trial, 38% patients were withdrawn from the study due to warfarin intolerance [10,11]. While in amiodarone, withdrawl incidences due to intolerable side effects (less than 12% per year) were lesser than warfarin [12-14]. The contraindications to amiodarone (acute hepatitis and hyperthyroidism) are less common than warfarin [15]. Hence, conversion to NSR is the only best option available to patients who are intolerant or having contraindications to warfarin. More recently, the evidences suggest that diltiazem can enhance thrombolytic therapy.

We administered IV diltiazem 0.1mg/kg/h continuously following the bolus of 0.25mg/kg because a previous study demonstrated very promising results with this mode of doses [16]. Also myocardial injury during open heart surgery is mediated in parts by intracellular calcium overload which may be a possible reason for AF. By blocking transmembrane calcium movement, diltiazem provide myocardial protection specially during aortic declamping and in the early post-operative period.

Both diltiazem and amiodarone have a well established role in the management of cardiac arrhythmias in non surgical setting. In a study between amiodarone and digoxin, use of IV amiodarone was found relatively safe and more effective than IV digoxin for heart rate control and conversion to normal sinus rhythm [17]. In a comparative study, diltiazem was found to be as effective as amiodarone in reducing early AF recurrences but it was found less effective in determining spontaneous or electric conversion with higher recurrence rate at 2 month. The author suggests that diltiazem pretreatment could be considered in those patients in whom amiodarone is contraindicated [18]. In our study we observed significant decrease in incidence of AF in both amiodarone and diltiazem group in compare to placebo. The requirement of DC shock for cardioversion and amount of energy required for DC shock was significantly less in diltiazem group than amiodarone group.

In a study, author suggested that significant rate control can be achieved in critically ill patients with atrial tachyarrhythmia using either diltiazem or amiodarone. Although diltiazem allowed for significantly better 24h heart rate control, this effect was offset by a significantly higher incidence of hypotension requiring discontinuation of drugs. Author of that study suggested that amiodarone should be used as an alternative in patients with severe haemodynamic compromise [19]. In our study we did not observed higher incidences of hypotension in diltiazem group. It was because the doses we used were much lesser than the doses (25mg bolus followed continuous infusion of 20mg/h for 24h) used by the author of that study. Another reason may be that our patients were not as critically ill as their patients were. In a comparative study between diltiazem and metoprolol, diltiazem was found more effective than metoprolol in decreasing ventricular rate in patients with AF. No incidence of hypotension was observed [20].

The limitation of our study is small size of study population. Trials in future with more subjects participating in the study may aid in identifying the role of amiodarone and diltiazem in patients with rheumatic AF undergoing valvular heart surgery.

Conclusion

In this study we concluded that intraoperative use of intravenous amiodarone and diltiazem are safe and feasible in patients of rheumatic heart disease with AF undergoing valve replacement surgery. Both drugs are equally effective in converting rheumatic AF to NSR and both drugs significantly reduce the requirement of energy for DC shock. Diltiazem reduces the requirement of DC shock more effectively than amiodarone.

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