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Original Article

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Effect of prophylactic single dose parenteral amiodarone in mitral valve replacement surgery

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Abstract

***Background & Aims*:** Amiodarone is a purposive medicine useful in restoring sinus rhythm (SR) after cardiac surgery. The aim of the study was to evaluate the effect of prophylactic intraoperative single-dose intravenous amiodarone and to convert atrial fibrillation (AF) into normal sinus rhythm (NSR) in the patients undergoing valve replacement surgery.

***Materials & Methods*:** In this prospective and interventional study, 180 patients of ASA III (American Society of Anesthesiologist) classification between the ages of 18-60 years, posted for Rheumatic Mitral Valve Replacement were allocated randomly to two equal groups (Group-1 and Group-2). Their hemodynamics parameters, Pre and post pulse rate, ECG findings and incidence of AF and VT/VF and ICU, Hospital stay were noted. Data was analysed with SPSS v26 using chi-square test. A two-tailed *P value* of 0.05 or less was regarded as statistically significant.

***Results*:** In our study, we found that there was suggestive significance between both groups as regard to mean pulse rate changes after 5 and 10 minutes of induction ($P > 0.05$). At the end of surgery, there was developing atrial fibrillation in few patients and sinus rhythm in more ($P > 0.05$). Postoperative arrhythmias in the first 24 hrs, AF was seen in 9(10%) patients in the Group 1 compare to Group 2 49 (54.4%) ($P < 0.001$). In both groups as regard to Mechanical ventilation & ICU stay was of suggestive significance in amiodarone group ($P < 0.0001$).

***Conclusion*:** The incidence of post-operative AF among high-risk patients was significantly reduced by a prophylactic amiodarone treatment resulting in a shorter time of intensive care unit and hospital stay.

***Keywords*:** Atrial Fibrillation, Amiodarone, Normal Sinus Rhythm, Valve Surgery

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Introduction

Persistent Atrial Fibrillation (AF) after rheumatic valve replacement surgery is the most frequent arrhythmia found in clinical practice (1-4). After rheumatic mitral valve replacement surgery, morbidity of AF was 94%, and restoration of sinus rhythm without intervention accounted for only 6% (5,6) 8.3% of early and 12.2% of late cardiac death resulted from AF, and the incidence of thrombosis and stroke in patients with AF was 17 times higher than those in patients without AF. So, it is very important maintain sinus rhythm after valve replacement surgery (8,9). Atrial fibrillation usually develops within the first 72 h following cardiac surgery, and is often self-limiting. Within 48 h of acute onset of symptoms, approximately 50% of patients spontaneously convert to normal sinus rhythm. Thus, the relative risks and benefits of therapy must be carefully considered. The etiology of AF following cardiac surgery is similar to that in nonsurgical patients except that pericardial inflammation and increased adrenergic tone play an increasingly important role. Further, AF after surgery may be associated with transient risk factors that resolve as the patient moves out from surgery, and the condition is less likely to recur compared with AF arising in other circumstances. Immediate heart rate control is important in preventing ischemia, tachycardia-induced cardiomyopathy, and left ventricular dilatation. At our institution, amiodarone is frequently used as a first-line drug for treating AF after cardiac surgery.

This study is designed to evaluate the 'effect of prophylactic intraoperative single-dose intravenous amiodarone in patients with rheumatic mitral valve disease undergoing mitral valve replacement surgery' to convert AF into NSR, arrhythmia prevention potential of amiodarone after release of aortic cross clamp, and the duration of maintenance in sinus rhythm in patients undergoing valve replacement surgery.

Materials & Methods

The study was a prospective and interventional study. The ethics committee approval has been taken prior study. All the patients participating in the study have been clearly explained the purpose and nature of the study in the language they can understand. They have been included in the study only after obtaining a written informed consent. A cross-sectional analysis will be made at the time of presentation. We will collect the data of 1 year and analyze it statistically. We conducted a study on 180 patients of ASA III (American Society of Anesthesiologist) classification between the ages of 18-60 years, posted for Rheumatic Mitral Valve Replacement and were allocated randomly to two equal groups (Group-1 and Group-2).

Our inclusion criteria's are: Patients in the age range 18-60 years, scheduled for Rheumatic Mitral Valve Replacement to be performed under general anesthesia, ASA risk category III, known history of allergy, sensitivity or other form of reaction to Amiodarone, left atrium size ≤40cm, Patient willing to sign informed consent and Exclusion criteria's are: Patients with pregnancy, Thyroid disease, Heart rate of <50/min, NYHA IV, Sick sinus rhythm, Atrioventricular block, Elevated liver enzyme levels, Serum creatinine> 2 mg/dl, Receiving one or more of the following medications: cimetidine, phenytoin, cholestyramine and cyclosporine were not included in the study, Patients allergic to amiodarone or receiving amiodarone therapy were also excluded, Left atrium size between 40-50 cm.

Statistical Analysis:

Data was entered into the computer and analysed with SPSS v26 (IBM Inc., Chicago, IL, USA). Quantitative data were expressed as mean and standard deviation (SD) and were compared by an unpaired Student's test. Qualitative data were given as frequency and percentage (percent) and examined utilizing the chi-square test. A two-tailed *P* of 0.05 or less was regarded as statistically significant.

Results

Total 180 patients were divided into two groups, which was done through computer generated randomization. One group receiving amiodarone and other group is receiving placebo. Their demographic details are shown in the Table 1.

Table 1: Demographic Data: Age, Height, Weight & Sex

	Group 1 (N=90) Amiodarone	Group 2 (N=90) Saline	*P value*
Age	39.34 ± 9.48	39.21 ± 8.24	0.920
Height	160.71 ± 7.04	161.14 ± 6.92	0.678
Weight	56.54 ± 11.84	51.26 ± 8.93	0.001
Sex	M= 47 F= 43	M= 54 F= 36	--------

There was no statistically significant difference between both groups concerning mean pulse rate changes after 10 minutes of induction ($P > 0.05$). Similarly, there was no statistically significant difference between both groups regarding mean pulse rate changes after 5 and 10 minutes of Amiodarone infusion/saline infusion ($P > 0.05$) (Table 2).

Table-2: Hemodynamic Data [Preope & After Induction at 0, 5, and 10min]

Pulse/min	Group 1 (N=90) Amiodarone	Group 2 (N=90) Saline	*P value*
Preoperative	97.43 ± 13.88	99.35 ± 7.69	0.252
After induction at 0 time point	98.96 ± 17.03	100.74 ± 9.96	0.394
After induction 5 min later	96.33 ± 16.70	99.62± 9.99	0.11
After induction 10 min later	91.30 ± 13.71	96.72 ± 7.81	0.001
After Amiodarone/Saline infusion at 0 time point	91.90 ± 13.99	95.72 ± 8.86	0.030
After Amiodarone/Saline infusion at 5 min later	85.12 ± 11.76	91.76 ± 8.72	<0.001
After Amiodarone/Saline infusion 10 min later	82.86 ± 10.25	91.76 ± 7.14	<0.001
After off bypass at 0 time point	94.01 ± 16.03	95.15 ± 6.85	0.534
After off bypass 5 min later	94.13 ± 12.25	95.48 ± 6.98	0.363
After off bypass 10 min later	92.32 ± 11.56	96.55 ± 6.31	0.003
After off bypass 15 min later	91.88 ± 12.46	96.37 ± 7.03	0.003
After off bypass 30 min later	92.15 ± 10.77	96.36 ± 5.95	0.001

There was suggestive significance between both groups as regard to mean pulse rate changes after 10, 15 & 30 minutes after Off Bypass in Amiodarone& control group ($P>0.05$).

In Table 3, we have shown the there was a significant difference systolic pressure after induction and off bypass 5 min later compare to diastolic pressure.

Table 3: Systolic and Diastolic Blood Pressure [Preoperatively& After Induction 0, 5, and 10 Minutes]

Systolic blood pressure	Group 1 (N=90) Amiodarone	Group 2 (N=90) Saline	*P value*
Preoperative	105.04 ± 9.91	98.88 ± 4.01	<0.001
After induction at 0 time point	103.15 ± 5.42 10.98	98.04 ± 5.37	<0.001
After induction 5 min later	101.55 ± 7.94	98.13± 4.74	0.001

Systolic blood pressure	Group 1 (N=90) Amiodarone	Group 2 (N=90) Saline	*P value*
After induction 10 min later	100.53 ± 9.30	98.04 ± 4.98	0.027
After Amiodarone/Saline infusion at 0 time point	98.64 ± 9.31	96.33 ± 4.60	0.037
After Amiodarone/Saline infusion at 5 min later	95.41 ± 8.76	94.02 ± 4.96	0.195
After Amiodarone/Saline infusion 10 min later	97.11 ± 8.78	95.55 ± 4.54	0.138
After off bypass at 0 time point	93.66 ± 8.89	94.73 ± 4.87	0.320
After off bypass 5 min later	98.42 ± 9.08	95.84 ± 5.72	0.024
After off bypass 10 min later	101.28 ± 8.79	97.35 ± 5.99	0.001
After off bypass 15 min later	100.86 ± 9.16	96.40 ± 5.91	<0.001
After off bypass 30 min later	101.06 ± 6.79	96.57 ± 5.97	<0.001
Diastolic blood pressure			
Preoperative	66.17 ± 7.58	65.77 ± 3.87	0.656
After induction at 0 time point	66.35 ± 8.75	65.57 ± 5.14	0.468
After induction 5 min later	65.40 ± 6.80	65.51± 4.18	0.895
After induction 10 min later	64.64 ± 7.51	65.48 ± 4.32	0.357
After Amiodarone/Saline infusion at 0 time point	65.28 ± 7.69	65.37 ± 5.59	0.929
After Amiodarone/Saline infusion at 5 min later	62.86 ± 8.54	63.55 ± 6.32	0.540
After Amiodarone/Saline infusion 10 min later	62.91 ± 7.98	63.80 ± 5.86	0.396
After off bypass at 0 time point	57.86 ± 7.14	61.88 ± 5.40	<0.001
After off bypass 5 min later	60.35 ± 6.58	61.93 ± 4.91	0.070
After off bypass 10 min later	61.13 ± 6.57	62.80 ± 4.97	0.057
After off bypass 15 min later	62.75 ± 5.98	63.68 ± 4.61	0.243
After off bypass 30 min later	65.08 ± 4.76	64.82 ± 3.88	0.681

In both groups as regard to ECG at the end of surgery was of suggestive significance with few patients developing atrial fibrillation and more in sinus rhythm compared to the control (*P >0.05*) (Table 4).

Table 4: ECG at End of Surgery

ECG END OF SURGERY	Group 1 (N=90) Amiodarone	Group 2 (N=90) Saline	*P value*
ATRIAL FIBRILLATION	09 (10%)	52 (57.7%)	<0.001
SINUS RHYTHM	81 (90%)	38 (42.2%)	<0.001

Postoperative arrhythmias in the first 24 hrs, AF was seen in 9(10%) patients in the Group 1 in comparison with Group 2 as 49(54.4%), which is of suggestive significance (*P <0.001*) and were started with amiodarone infusion. Only 3(3.33%) and 1(1.1%) patient in the group 2 developed slow AF and ventricular ectopics, respectively, which is of no suggestive significance (Table 5).

Table 5: Postoperative Arrhythmias in 24hrs

	Group1(N=90) Amiodarone	Group 2 (N=90) Saline	*P value*
POST OPERATIVE ARRHYTHMIAS IN 24Hrs	09 (10%)	49 (54.4%)	<0.001
ATRIAL FIBRILLATION/AMIODARONE INFUSION			
SINUS RHYTHM	81(90%)	37 (41.1%)	<0.001
SLOW ATRIAL FIBRILLATION	00	03 (3.3%)	0.242
VENTRICULAR ECTOPICS	00	01 (1.1%)	1.000

Patient requiring ventricular rate control in post-operative sustained AF is lower in group 1 than group 2 which is statistically significant (*P<0.0001*) (Table 6).

Table 6: Requirement of Ventricular Rate Control(>90/Min.) In Postoperative Operative Sustained AF

	Group 1 (n=90) Amiodarone	Group 2 (n=90) Saline	*P value*
	>90 PULSE RATE	>90 PULSE RATE	
Post-operative sustained AF	8(8.8%)	49(54.4%)	<0.0001

In both groups as regard to Mechanical ventilation & ICU stay was of suggestive significance (*P* <0.0001) (Table 7).

Table-7. Time of Mechanical Ventilation & ICU Stay

	Group 1 (n=90)	Group 2 (n=90)	*P VALUE*
Mechanical ventilation(hrs)	7.64 + 1.24	9.21 ± 1.81	<0.0001
ICU stay(hrs)	46.91 ± 2.78	56.11± 6.07	<0.0001

Discussion

The purpose of this study was to evaluate the efficacy and safety of parental use of injection amiodarone in a prophylactic dose of 3mg/kg in patient with rheumatic heart disease posted for mitral valve replacement surgery to prevent post-operative arrhythmias especially Atrial Fibrillation.

Despite significant progress in terms of heart surgery in the last 50 years, AF after cardiac surgeries is still the most common complication. It may often cause prolonged ICU and hospital stay after surgical treatment (10). As reported in the literature, AF occurs most frequently in the first week postoperatively, and the incidence ranges between 30% and 60% (11). Although it usually does not cause postoperative mortality, AF often can induce hemodynamic impairment and thromboembolic events, and requires antiarrhythmic therapy. Because AF extends the duration of ICU and hospital stay, it accounts for the increased hospital costs (10,12). In our study same result found that preop amiodarone infusion can lead to controlled arrythmias and incidence of AF and lead to less ICU and Hospital stay compare to placebo.

Patients with mild atrial fibrillation may have disturbance of hemodynamic in the perioperative period, and patients with severe atrial fibrillation may have severe heart failure, stroke, and cardiogenic shock or even die. Studies found that improving the conversion

rate of atrial fibrillation and maintaining sinus rhythm was the key after rheumatic heart disease associated valve replacement (10,11). In our study we have found that after amiodarone infusion the hemodynamic data are significantly decreased after induction and off bypass compare to placebo.

In all of the studies, the amiodarone therapy was well tolerated and appeared to reduce the occurrence of post-operative AF. Amiodarone treated patients had a low number of side effects without a significant difference compared with the placebo-treated patients. The reason for the low number of side effects might be the short amiodarone treatment for eight days.

The recent publication of a large randomized trial of amiodarone arrhythmia prophylaxis after cardiac surgery (PAPABEAR) is of great interest (13). It was striking how similar the results of this trial are similar to our analysis of perioperative amiodarone during mitral valve repair (14), and a detailed comparison raises several points. First, both studies concluded that amiodarone was effective, reducing postoperative atrial arrhythmias by half and virtually eliminating mortality from ventricular arrhythmias. Second, serious complications of a brief perioperative administration were rare. In PAPABEAR, bradycardia requiring dose reduction occurred in 5.7% of cases and was considered a side effect. In clinical practice, however, postoperative bradycardia can be managed easily with transient atrial pacing, and reduction to a low discharge dose is routine.

The onset of antiarrhythmic effects of oral amiodarone takes 7-10 days; complete antiarrhythmic effects may not be noticed for up to 10 weeks. However, the onset of the antiarrhythmic effects of intravenous amiodarone are rapid (15,16). Low-dose oral amiodarone was found to be safe and effective in restoring and maintaining NSR after balloon mitral valvotomy in patients with AF and RHD (15,16). Short-term amiodarone (high oral dose) with or without electrical cardioversion was effective and safe in the treatment of chronic rheumatic AF after mitral valve surgery. Prophylactic oral amiodarone was shown to reduce the incidence of new-onset AF in patients undergoing open heart surgery (17,18). However, literature is scarce on the therapeutic role of intravenous amiodarone in the treatment of chronic rheumatic AF in patients undergoing for mitral valve surgery. Benefit of amiodarone in restoring NSR was concluded in previous studies on Coronary Artery Bypass Grafting patients, which used more or less different protocols for giving amiodarone.

This study represents another trial that aiming at finding out if a single perioperative (pre-CPB) loading dose of amiodarone can decrease the incidence of postoperative new-onset AF in a group of patients undergoing valvular surgery with non-compromised cardiac function. Our findings confirm the same. This easy regime allows more patients to be treated.

This study is in accordance with Selvaraj et al. (19), Yasser Mohamed Amr et al. (20), and Sandeep Kumar Kar et al. (21), with the same dose of amiodarone 3 mg/kg in 50ml normal saline was started as intravenous infusion through the central venous route over a period of 10 min prior to incision. Studies dealing with IV amiodarone indicate the time and dose dependent mechanism of the rhythm conversion in patients with AF, but no optimal dose of the drug has been recommended. Our regimen, with a relatively low dose of amiodarone, has proved to be effective with minimal adverse reactions. Therefore, it may be hypothesised that the smaller dose is safer in termination of AF. In this study no significant difference in the basal heart rate has been observed except for 10 min post induction 91.3±13.71 in amiodarone group and 96.72±7.8 in the control group ($P = 0.001$). Our study is in accordance with Selverajet et al. (19) where there was no significant difference in the mean basal heart rate and with Sandeep Kumar Kar et al. (21) there was no significant difference in the basal heart rate 101.25 ± 12.3 in amiodarone group and 108.89 ± 11.4 in the control group ($P = 0.24$).

In our study, significant changes have been noted in mean HR after 5 and 10 min of amiodarone infusion85.12±11.76/min and 82.86±10.25/min with regard to the control group 91.76±8.72/min and 91.16±7.14/min ($P<0.001$). In this context, the study is in accordance with Selvaraj et al. (19) where the difference in the HR before and 5 min after drug

infusion in the amiodarone group was +9.55 (±13.59)/min ($p < 0.001$) more than the difference in the HR before and 5 min after drug infusion in the control group (±6.3)/min. In our study, there was suggestive significance in mean HR at 10, 15 and 30 min after off bypass in amiodarone group compared to the control group ($P > 0.05$).

No patient developed bradycardia during infusion of amiodarone or placebo in our study, which is in accordance with Selvaraj et al. (19), where two patients had bradycardia during the infusion of amiodarone; however, this was statistically not significant (p = 0.162) nor in Sandeep Kumar Kar et al. (21) where there was no incidence of bradycardia in any of the patients during the infusion of the study drug or the placebo leading to cessation of the infusion or treatment.

In this study significant hypotension with the control group has been observed at 5 min after induction (P 0.001) and at 10, 15 and 30 min after off bypass (P> 0.05). By contrast, there was no hypotension in any of the patients of both the groups during the infusion of the drug or the placebo in the Selvaraj et al. study (19).

Even in the study done by Sandeep Kumar Kar et al. (21), there was no incidence of bradycardia in any of the patients during the infusion of the drug or the placebo leading to cessation of the infusion or treatment.

In this study, upon the release of the Aortic cross clamp, NSR has been observed in 79 patients (87.7%) in the amiodarone group as opposed to 46 patients (42.2%) in the control group (P< 0.001). which is in accordance with Selvaraj Et al 19 where NSR was observed in 31 patients (73.8%) in the amiodarone group and in 17 patients (58.5%) in the control group. In this study, on release of ACC, AF was seen in 7 patients (7.7%) in the amiodarone group and in 46 patients (51.1%) in the control group, which is statistically significant (P< 0.001). However, none of the patient reverted to sinus rhythm, neither during cardioversion or amiodarone loading or infusion.

Conclusion

The present study concluded that, Injection of amiodarone 3mg/kg in 50ml saline compared to same amount of saline infusion intravenously in the patients with rheumatic Mitral valve disease undergoing Mitral valve replacement surgery showed: A): hemodynamic stability was present before and after infusion with very little variability after cardiopulmonary bypass, B): More NSR seen in majority of patients with very few patients developing AF after cross clamp removal, C): Extent of patient developing VF/VT were lower after cross clamp removal, D): Decreased amount of defibrillation/cardioversion required after cross clamp removal, E): Decreased incidences of AF or any other arrhythmia and complications or side effects at the end of surgery and in the first 24hrs of surgery, F): Lower extent of using any antiarrhythmic drugs intraoperatively and postoperatively, G): Shorter duration of requirement of temporary pacing, H): Amiodarone has enhanced the ventricular rate control in post-operative sustained AF, I): Mechanical ventilation and ICU stay are exponentially decreased in patient receiving amiodarone, and J): Chances of having post-operative stroke are seen in elderly patients, but are low in both the groups.

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Conflict of interest

The study was conducted without any conflicting interests from the authors.

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Data availability:

The raw data supporting the conclusions of this article are available from the authors upon reasonable request.

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