Evaluation of early direct current cardioversion for maintenance of sinus rhythm in rheumatic atrial fibrillation following successful balloon mitral valvotomy

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ABSTRACT

Background: Patients with rheumatic mitral stenosis (MS) and atrial fibrillation (AF) are at risk for thromboembolism and restoration of sinus rhythm (SR) may be the preferred strategy. Percutaneous balloon mitral valvotomy (PBMV) improves hemodynamics, but may not be enough to restore SR.

Methods: Prospective randomized study aimed at evaluating efficacy of early direct current cardioversion (DCCV) following successful PBMV in patients with long-standing AF. Group 1 (n = 20) had patients of rheumatic MS with AF who underwent successful PBMV. Group 2 (n = 15) patients were DC cardioverted and administered oral Amiodarone for 6 weeks. Primary endpoint was maintenance of SR after 6 months. Secondary endpoints were functional capacity, number of embolic episodes, adverse drug effects, and all-cause mortality.

Results: In Group 2, all patients underwent successful cardioversion. At a mean follow-up of 7.6 months, 95% in Group 1 were in AF. In Group 2, 87% patients were in SR and 13% had reverted to AF. Difference in rate of SR was 0.82 (95% CI 0.2, 1.01) (p = 0.001), with relative risk of 7.1 (1.95, 25.9, 95% CI, p = 0.001) for patients to be in AF who underwent only successful PBMV, i.e. Group 1. There was significant improvement in quality of life (SF36) score in Group 2 (p = 0.001), with no deaths, stroke, or adverse drug effects in either group.

Conclusion: In patients with rheumatic MS and AF, early DCCV and a short-duration oral Amiodarone, following successful PBMV, may be a reasonable strategy to attain long-term SR.

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1. Background

Rheumatic heart disease (RHD) still retains its dubious distinction amongst the important acquired heart diseases in developing countries, affecting young adults and accounting for about 25% of all patients with heart failure in endemic countries. The estimated prevalence of RHD is 20 per 1000 among young adults (20–35 years), with 62–78 million estimated cases worldwide, with 1.4 million deaths yearly from RHD and its complications. 

Increased transmital gradient causes raised left atrial (LA) pressure leading to LA enlargement, causing pulmonary venous and arterial hypertension and right-sided heart failure. In addition to gradual progression, 50% patients have episodes of acute deterioration due to paroxysmal or chronic atrial fibrillation (AF) with rapid ventricular rate, causing pulmonary edema, acute decompensated heart failure, and cardioembolic phenomenon. Persistent AF frequently complicates mitral stenosis (MS) and conveys unfavorable long-term prognosis. Over 80% patients with MS with systemic embolism are in AF, commonest embolic site being the cerebral circulation. High risk of thromboembolism in such a subset of patients renders restoration of sinus rhythm (SR) to be the preferred strategy over rate control.

Persistent AF leads to the deleterious atrial remodeling, which perpetuates sustenance of AF. However, it has been seen that atrial remodeling is not a permanent phenomenon and may be reversed. It has been proposed that relieving MS will reduce LA dilatation, and thus may lead to reverse atrial remodeling by changing the hemodynamics. Previous reports demonstrate significant reverse atrial electrical remodeling in patients with MS after percutaneous balloon mitral valvotomy (PBMV). PBMV or surgery is effective in relieving MS with correction of hemodynamic alterations, but it often fails to restore SR. In previous series, surgical correction of mitral valve disease in patients with AF resulted in spontaneous conversion to SR in 46%; however, rate of spontaneous conversion was much lower in other reports. Many studies have attempted various strategies of rhythm control in patients with rheumatic AF after PBMV, including oral Amiodarone and direct current cardioversion (DCCV), with varying success. However, these studies also had a time lag between performing percutaneous transvenous mitral commissurotomy (PTMC) and DCCV, probably to see whether Amiodarone alone can lead to successful pharmaco-cardioversion and to allow further improvement in hemodynamics. These studies had indicated that smaller LA size, shorter AF duration, and absence of involvement of other valves were important predictors for conversion of AF and in maintenance of SR over long term. The safety profile of Amiodarone, with its interaction with oral anticoagulants (OAC), also is a major factor which prevents its long-term use.

No study till date has prospectively evaluated Indian patients with severe MS of prolonged duration with enlarged LA and long-standing AF with early DC cardioversion as a rhythm control strategy post-PBMV. This randomized prospective study was devised to evaluate efficacy of early DCCV followed by oral Amiodarone in treatment of rheumatic MS and AF post-PBMV during the index hospitalization.

2. Material and Methods

This study is a prospective randomized study performed at AIIMS, New Delhi from January 2012 to July 2013. Ethical approval was taken from the institutional ethical committee. The study included patients with rheumatic MS and AF fulfilling the criterion for PBMV according to American College of Cardiology/American Heart Association guidelines. Other inclusion criteria were patients above 18 years, with AF on electrocardiogram (ECG) at least twice with minimum of 2-week interval. Exclusion criteria were patients less than 18 years, contraindications to anticoagulation or Amiodarone use; or requirement for surgery because of complications from PBMV, inability to comply with 6-month follow-up, and patients not giving written consent for participation in the study. Patients were randomized in two groups by computerized method at the time of enrollment. The flow of participants in the study is shown in Fig. 1.

Informed consent was taken from all eligible patients. Baseline historical and clinical parameters were noted at enrollment. Patients’ functional status was assessed by New York Heart Association (NYHA) classification and quality of life (QOL) was assessed by modified Medical Outcomes study Short-form Health survey (SF-36) questionnaire (modified for Indian population). Patients on OAC were advised to

Fig. 1 – Flowchart of the study.
discontinue drug 5 days before PBMV. Transthoracic echocardiography (with iE33; Philips Medical Systems, Bothell, Washington)/transesophageal echocardiography (when needed) was performed a day prior to PBMV and repeated before DCCV. Following echocardiographic parameters were recorded at the time of enrolment: LA size, presence of LA/LA appendage thrombus, mean and end transmural pressure gradient, mitral valve area (MVA) (by pressure half-time technique/planimetry), Wilkins’ score of mitral valve, presence and severity of mitral regurgitation (MR), to rule out severe aortic valve stenosis/ regurgitation and tricuspid regurgitation (TR), and right ventricular systolic pressure from TR jet velocity.

In Group 1, patients with rheumatic MS with AF underwent successful PBMV. PBMV was performed by transseptal antegrade approach using Inoue balloon technique.18,19 Appropriate balloon sizing was done based on the Hung’s formula. Hemodynamic and catheterization data, including LA pressure, right atrial pressure, right ventricular systolic pressure, pulmonary artery pressure, and transmural mean pressure gradient, were obtained before and immediately post-PBMV. Procedural success was defined by absolute post-PBMV MVA ≥1.5 cm² or ≥50% increase in MVA and MR not more than 2+ as per Sellers’ classification.

In Group 2, patients, following PBMV, were loaded with standard intravenous dose of Amiodarone (150 mg iv bolus over 10 min) on day of PBMV followed by iv infusion of Inj Amiodarone (1 mg/kg/min for 6 h followed by 0.5 mg/kg/min for 18 h). The next day, these patients underwent DCCV. Protocol for DCCV was maximum of 3 synchronized, biphasic shocks of increasing energy of 100 J, 200 J, and 200 J, respectively given under sedation with weight-based Inj Midazolam or Propofol for sedation with biphasic cardioverter with standard transcutaneous patches placed in antero-lateral position in a CCU setting. In patients who failed conversion at first attempt, second attempt was planned at 4 weeks. Oral Amiodarone was continued at 200 mg twice a day for 5 days and then 100 mg once daily till 6 weeks to cover the blanking period. Oral Amiodarone was planned to be discontinued if patient develops side effects.

In both groups, patients were on monthly follow-up to monitor the rhythm. ECG was done at every visit. OAC was continued in both groups throughout the study period, with target international normalized ratio between 2 and 3. At each visit, patients’ functional capacity and symptoms of heart failure according to NYHA classification and episodes of systemic emboli were noted. The improvement in QOL was assessed at the end of follow-up period by the SF-36 questionnaire. All patients were prospectively and intensively monitored for side effects, including immediate and late complications of PBMV, DCCV, and various adverse effects of Amiodarone/OAC. Patients in both groups were administered digoxin and other rate control drugs as per treating physicians’ discretion.

2.1. Outcomes

Primary outcome measure was the rate of SR at the end of follow period of study. Secondary endpoints were improvement in functional class (NYHA), QOL, occurrence of stroke, and death and complications of OAC/Amiodarone.

2.2. Statistical analysis

Data were presented as numbers (%) or mean ± SD, as appropriate. Baseline characteristics were compared between two groups using Chi-square test (categorical)/t-test for independent samples (continuous) as appropriate. Primary outcome of rate of SR/AF between groups was compared using two samples proportions test. Changes in NYHA status was compared between groups using Fisher’s exact test. Change in SF36 status was compared using Wilcoxon test. Hemodynamic parameters were compared between groups using t-test for independent samples and change from baseline within group was tested using paired t-test. The p-value less than 0.05 was considered as statistically significant. Statistical analysis was carried out using Stata 11.0 (College station, TX, USA).

3. Results

Patients were well matched for baseline characteristics in both the groups with similar pre- and post-PBMV echocardiographic parameters, as shown in Table 1. None of the patients in either group had development of significant MR after PTMC.

Patients had symptomatic chronic AF for an average of 24.3 months. This duration of AF was calculated from time patients developed symptoms associated with AF and from previous documented ECG evidence. All patients in both groups underwent successful PTMC with significant improvement in MVA (Group 1: 0.79–1.74 cm², p = 0.001), (Group 2: 0.77–1.82 cm², p = 0.001) and indexed LA volume (Group 1: 55.9–24.1 cm², p = 0.001) and (Group 2: 66.7–29.2 cm², p = 0.001).

At end of follow-up period (range 6–9 months), 19 patients (95%) in Group 1 were still in AF, while 1 (5%) patient in this group had reverted to SR spontaneously during the second week. In Group 2, 13 (87%) patients continued to remain in SR, while 2 patients (13%) had reverted back to AF, one at 2 weeks and one at 4 months, as shown in Fig 2. The difference (95% CI) in rate of SR in both groups is 0.82 (0.2, 1.01), p = 0.0001, as shown in Table 2. The risk for patients to be in permanent AF who undergo only PBMV without any attempt to reversion and maintenance of SR is 7.1 times (95% CI 1.95, 25.9), p = 0.001.

At end of follow-up, change in patient’s functional status as assessed by NYHA class was not statistically significant (p value = 0.213). The QOL, as assessed by SF-36, showed similar scores at baseline in both groups (p > 0.05), which were significantly lower when compared to healthy Indian population (data provided by earlier study).20 At 6 months, there was improvement in scores in both groups with scores of Group 2 significantly better (p = 0.001-0.004), indicating better QOL in rhythm control group, as shown in Fig 3.

No patients were lost to follow-up. No secondary outcomes of death, stroke, embolism, and complications related to OACs/Amiodarone use were seen in either group.

In Group 2, post-PBMV, all patients had successful cardioversion to SR by synchronized biphasic shocks. 8 patients required single 100 J biphasic shock, 3 patients required 2 shocks (1 × 100, 1 × 200 J), and 4 patients required 3 shocks (1 × 100, 2 × 200 J). There was no primary failure of DCCV.

The mean heart rate in both groups was similar on follow-up (p = 0.41).
4. Discussion

To the best of our knowledge, this study is the first randomized trial to evaluate the efficacy of early DCCV along with intravenous loading dose followed by low-dose short duration Amiodarone (06 weeks) in the treatment of rheumatic MS and long-standing AF (duration >12 months) after successful PBMV.

Long-standing AF leads to remodeling with persistent alterations in properties and functions of atrial tissue with
changes in electrical, structural, and contractile elements. Reduced atrial contractility, development of fibrosis, and atrial enlargement are key characteristics of atrial structural remodeling.\textsuperscript{10} Rheumatic MS causes increased LA pressure leading to atrial stretch.

This increase, associated with changes in refractory period and conduction velocity, make atrial substrate conducive for maintaining many atrial re-entry circuits leading to sustainability of AF. This phenomenon is associated with electrical remodeling due to alteration in ion channel expression and functioning. Ca\textsuperscript{2+} current inactivation and I\textsubscript{CaL} downregulation and inward rectifier K\textsuperscript{+} current enhancement decrease Ca\textsuperscript{2+} loading by reducing action potential duration. These changes stabilize atrial reentry rotors, increasing AF vulnerability and sustainability.\textsuperscript{10} Electrical remodeling contributes to several clinically important phenomena, including early AF recurrence after cardioversion.

Cardioversion acts on atrial myocytes with irregular firing foci, by simultaneous elective depolarization and resetting the sinus node to act as a dominant pacemaker, leading to initiation of atrial reverse remodeling process. AF recurrence after DCCV can be tackled by administration of antiarrhythmic drugs to support reverse electrical remodeling. Removal of trigger for atrial stretch by PTMC leads to hemodynamic changes, which initiate atrial structural reverse remodeling.\textsuperscript{11} Decrease in LA volume and mean LA pressure accompanied by shortening of p wave duration were observed after PBMV, indicating the process of reverse electrical and structural remodeling, which reduced the vulnerability for occurrence of sustained AF.

Hemodynamic parameters in both groups (pre- and post-PBMV) have been comparable, suggesting that PTMC alone does not significantly cause spontaneous cardioversion to SR. LA indexed volume was significantly reduced at 6 months, as compared with baseline in both groups, indicating that reduction in LA dimension after successful PBMV helps to maintain SR but is not sufficient for reverting long-standing AF to SR, and additional measures should be taken to restore SR.

Amiodarone was continued in low doses for short term only to facilitate early electrical reverse remodeling. PBMV followed by early DCCV, along with short-duration antiarrhythmic use in patients with long-standing AF, may cause simultaneous electrical and structural reverse atrial remodeling and thus benefits cardioversion of AF and maintenance of SR over longer duration. Our study showed that short-duration Amiodarone was well tolerated with no adverse effects necessitating discontinuation of treatment. Discontinuation

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**Table 2 – Primary outcome of rate of SR/AF in both groups.**

| Follow-up at 6 months | Group 1 n = 20 (%) | Group 2 n = 15 (%) |
|-----------------------|-------------------|-------------------|
| Patients in AF        | 19 (95.0)         | 2 (13.0)          |
| Patients in SR        | 1 (05.0)          | 13 (87.0)         |
| Difference (95% CI)   | 0.820 (0.2, 1.01) | p = 0.0001        |
| RR (95% CI)           | 7.1 (1.9, 25.9)   | p = 0.0001        |

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**Fig. 3 – QOL assessed by SF-36 at Baseline and after 6 months. PF - physical functioning; RP - role limitations due to physical health problems; BP - bodily pain; GH - general health; VT - vitality, energy and fatigue; SF - social functioning; RE - emotional problems; MH - mental health.**
of Amiodarone at 6 weeks did not cause recurrence of AF during the follow-up period.

In the study by Hu et al., 96% patients maintained SR on continued low-dose Amiodarone therapy (100–200 mg/day, mean maintenance dose of 130 mg/day at 24 weeks and 121 mg/day at 52 weeks) for a duration of 1 year (with side effects including thyroid abnormalities despite low dose). Another trial, which evaluated patients of AF with RHD, including multivalvular involvement and post-operative cases with rhythm control strategy by DCCV, showed that a conversion rate to SR was around 85%, of which only 52% patients maintained SR at 1 year despite long-term Amiodarone therapy.14 In another study, when DCCV was attempted at one month after PBMV, while on oral Amiodarone, successful DCCV was achieved only in 71% patients and AF recurred in 48% patients on follow-up despite long-term Amiodarone.15 This study also documented adverse effects of long-term oral Amiodarone. In this study, an early DCCV followed by oral Amiodarone, as in our study, led to a better conversion to SR and maintenance of SR in Group 1 suggesting a greater role of an early DCCV. This translated into lesser hospital and patient costs by allowing early discharge and avoiding readmission for DCCV at a later date.

Our study showed that maintenance of SR lead to better functional class as seen by improvement in NYHA class (however, statistically NS p > 0.05). The QOL as assessed by SF36 showed significant improvement in patients with SR, as compared to the PTMC-only group (p = 0.001–0.004). During the follow-up period, no cardioembolic events were noted in both groups, neither any adverse effects of OAC occurred. This finding may be confounded because period of follow-up was short and patients were still on OACs.

We, hereby, demonstrated that electrical and structural reverse remodeling can be initiated successfully simultaneously, by performing PBMV followed by DCCV within a short interval. This may be important in developing countries where patients may not have facility for repeated or prolonged hospitalization.

The benefits of maintenance of SR in rheumatic MS with AF are improvement in ventricular function by reversing atrial cardiomyopathy, prevention of blood stasis in LAA and LA, thus preventing thrombus formation, and reduction in cardioembolic complications.16 Short duration of antiarrhythmic drug therapy reduces complications associated with administration of long-duration antiarrhythmics. Amiodarone has significant long-term toxic effects and drug interactions with OAC, digoxin, etc., and it may be safer to discontinue this drug as soon as possible.

The limitation of our study is small numbers of patients and short follow-up. Also, we did not study occurrence of paradoxical AF in study groups since it was not part of our protocol.

5. Conclusion

In patients with rheumatic MS with AF, after successful PBMV, it is possible to achieve and maintain SR by an early DCCV and short-term antiarrhythmic drug administration. Patients benefited from restoration and maintenance of SR demonstrated by improvement in functional class and improvement in QOL. Early rhythm control by DCCV should therefore be considered as a feasible and safe therapy for patients with rheumatic MS with long-standing AF after PBMV. In addition to the clinical benefits, early DCCV strategy, by doing away with readmissions, not only decreases the cost but also adds to the convenience.

Conflicts of interest

The authors have none to declare.

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