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Feasibility of aspirin in primary prevention of stroke in rheumatic heart disease and sinus rhythm

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Abstract

Background: Thromboembolism is frequently seen in patients of rheumatic mitral stenosis with atrial fibrillation. It is however, not uncommon in those with sinus rhythm. Since anticoagulants are not routinely recommended in rheumatic mitral stenosis patients with sinus rhythm, antiplatelet therapy may be considered as a preventive means.

Methods: Patients with rheumatic mitral stenosis [mitral valve area < $2cm^2$], in sinus rhythm and at least1 additional risk factor for embolism (severe MS, left atrial size greater than 50 mm, spontaneous echo contrast and significant aortic regurgitation) were enrolled. Exclusion criteria included a history of stroke/ transient ischemic attack, systemic embolism or oral anticoagulation. Daily dose of 75 mg of enteric coated aspirin was prescribed. Follow- up was done at every 3 months telephonically and 6 months in the out-patient clinic. The primary outcome was composite of major and non-major bleeding. The secondary outcome was composite of stroke/ transient ischemic attack, or systemic embolism.

Results: 275 patients with mean age of 34.8 ± 11.8 years were enrolled. Patients were followed-up for a mean duration of 8.2 months. No bleeding complication was observed. No patient developed stroke/ transient ischemic attack, or systemic embolism. 67 patients were non-compliant to aspirin.

Conclusion(s): Aspirin is safe and well tolerated in patients with rheumatic mitral stenosis in normal sinus rhythm who are at risk for cerebral and non-cerebral thromboembolism.

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Key Words: Aspirin; Antiplatelet, Thromboembolism, Rheumatic mitral stenosis, Atrial fibrillation, Normal sinus rhythm

Introduction

Thromboembolism is a frequent occurrence in patients with rheumatic mitral stenosis(1,2). Atrial fibrillation (AF) is an important risk factor for systemic thromboembolism in these patients. However, the risk of thromboembolism in rheumatic mitral stenosis (MS) patients with sinus rhythm may not be insignificant(3,4).Factors such as small mitral valve area, large atrial size, higher age and transient subclinical AF are proposed as possible risk factors in such patients(5,6). There is lack of unanimity in the current practice guidelines regarding anticoagulation in rheumatic MS patients with sinus rhythm(7,8). Antiplatelet therapy represents an attractive prospect in such patients. The present study was performed to assess the safety and feasibility of aspirin in this subgroup of patients.

Methods

Patients attending the cardiology outpatient clinic at a tertiary care teaching hospital in North India were assessed for eligibility. Patients were prospectively enrolled if they were >18 years of age with rheumatic MS (mitral valve area <2 cm^2 on transthoracic echocardiography) as an isolated or dominant lesion, were in sinus rhythm and had at least 1 risk factor for embolism (severe MS, left atrial size greater than 50 mm, spontaneous echo contrast in left atrium and significant aortic regurgitation). Patients were excluded if they had a history of stroke/ transient ischemic attack (TIA), systemic embolism or were receiving oral anticoagulation at enrollment. Patients with documented past episodes of AF were also excluded. The study was approved by institute ethics committee (Approval Number: IECPG-477/21.08.2016). Written informed consent was obtained from all participants and the study protocol conforms to the ethical guidelines of the 2013 Declaration of Helsinki.

A careful history was obtained and a focussed physical examination was obtained from all study participants. A 12-lead electrocardiogram was obtained at study entry. All patients underwent transthoracic echocardiography (iE33, Philips Medical Systems, Bothell WA, USA) using standard protocols. Mitral valve area (MVA) was estimated using continuous-wave doppler by the pressure half-time method, supplemented by estimates obtained using planimetry. Left atrial dimensions were measured in the parasternal long-axis and apical 4-chamber views. The left atrial appendage was visualized in the basal short-axis and 2-chamber views. Spontaneous echocardiographic contrast (SEC, dynamic smoke-like echoes) in the left atrium was documented.

All patients enrolled in the study received 75 mg of enteric coated aspirin daily. The primary outcome of interest was the composite of major and non-major bleeding. Major bleeding was defined according to International Society on Thrombosis and Hemostasis (ISTH) definition as a fatal bleeding and/or symptomatic bleeding in a critical area or organ such as intracranial, intraspinal, intraocular, retroperitoneal, intra-articular or pericardial, or intramuscular with compartment syndrome, and/or bleeding causing hemoglobin drop of 20g/L or more, and/or blood transfusion of 2units or more(9). Non-major bleeding was defined as any sign or symptom of hemorrhage that did not fit the criteria for major bleeding but required medical intervention by a healthcare professional or led to hospitalization or prompted a face to face evaluation(10). The secondary outcome of interest was the composite of stroke/ TIA, or non-CNS systemic embolism. Stroke was defined as any focal neurologic deficit that lasted >24 hours with or without brain imaging suggestive of a primary ischemic origin leading to tissue infarction. TIA was defined as a physician-diagnosed focal neurologic deficit consistent with ischemia in a vascular territory, lasting <24 hours without tissue infarction. The diagnosis of non-CNS systemic embolism was made clinically(loss of arterial pulse or evidence of end-organ ischemia) and confirmed by imaging studies where appropriate. Patients were followed up once every 3 months telephonically and every 6 months in the out-patient clinic. In the event that patients were evaluated at other hospitals during follow-up,

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details of clinical and imaging findings were obtained from the treating physician. Patients were followed up for a period of 1 year.

Statistical Methods:
Data was recorded on a predesigned proforma and managed on an excel spreadsheet. All the entries were checked for any possible keyboard errors. Categorical variables were summarized as frequency (percentage). Quantitative variables were assessed for approximate normality and summarized as mean ± SD**.** All analyses were performed using Stata version 11 (StataCorp LLC, College Station, TX, USA).

Results
A total of 320 patients were screened between August and December 2016. 275 patients who met the inclusion and exclusion criteria were enrolled in the present study (Figure 1).

The mean age of study participants was 34.8 ± 11.8 years. Majority of study participants were females. Most patients were in NYHA I/ II functional class (Table 1). 95% patients had severe mitral stenosis on echocardiography. Associated significant mitral regurgitation was present in 22% of patients. The mean left atrial diameter was 42.9 ± 6 mm. Spontaneous echocardiographic contrast was seen in 2.5% of patients. 19% patients had associated significant AR (Table 1).

8 patients were lost to follow-up. 67 patients were non-compliant to aspirin (Table 2). 14 patients developed atrial fibrillation on follow-up and were prescribed oral anticoagulation.36 and 13 patients underwent balloon mitral valvuloplasty (BMV) and mitral valve replacement respectively during follow up. 3 patients died during the study period in our hospital, of which 1 patient died during the post-operative period due to sepsis and 2 patients died due to refractory heart failure with superimposed lower respiratory tract infection.

In the present study, the primary outcome of major and non-major bleeding was not observed in any patient. No patient developed stroke/ TIA, or non-CNS systemic embolism during follow-up.

Discussion
The present trial showed that low dose aspirin is safe and well tolerated in patients with rheumatic mitral stenosis in sinus rhythm who are at risk for cerebral and non-cerebral thromboembolism. There were no episodes of major or non-major bleeding with the use of low dose aspirin in the present study.

Systemic thromboembolism (cerebral and non-cerebral) is a major complication in patients with rheumatic mitral stenosis. Atrial fibrillation is present in approximately 40% of these patients and increases the risk of thromboembolism manifold(2,11–14). Although the risk of thromboembolism in patients with rheumatic mitral stenosis is increased by the presence of concomitant atrial fibrillation, the risk in patients with sinus rhythm may not be negligible(3,4). Various factors such as small mitral valve area, large atrial size, increasing age, inflammation and transient subclinical AF are proposed as possible risk factors in such patients(5,6,15–17).The role of anticoagulation in these patients is debatable. Although these drugs are effective in preventing thromboembolism, given the relatively low risk in patients with sinus rhythm and the risk of bleeding with these agents, the risk benefit ratio with oral anticoagulation may not be favorable in all cases. Oral anticoagulant use in developing countries is further limited by the modest time in therapeutic range (TTR) and difficulty in monitoring INR(18). In addition, transient atrial fibrillation may not be documented in all such cases given the low rates of extended ECG monitoring and there may be a hesitation on part of the treating physician to use oral anticoagulation in the absence of documented atrial fibrillation(18). Antiplatelets may represent an alternative therapy in rheumatic mitral stenosis patients with sinus rhythm. The use of antiplatelets in these patients may not be without rationale. Using electron microscopic studies, Riddle et al. showed increased platelet reactivity

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in patients with valvular heart disease including those with mitral stenosis(5,6,15). In another study from Japan, Kunishima and colleagues demonstrated increased platelet activation in patients with rheumatic heart disease (63% had rheumatic mitral stenosis) compared to healthy controls(20). Severity of mitral stenosis may be associated with the extent of platelet activation in rheumatic mitral stenosis. Chen et al. demonstrated an increased regional left atrial platelet P-selectin expression suggestive of platelet activation. The regional left atrial P-selectin expression had a direct relationship with the severity of mitral stenosis(21)**.** However, data on the use of antiplatelet therapy in patients with rheumatic mitral stenosis is scant. Steele et al. studied the effect of sulfinpyrazone in patients with rheumatic mitral stenosis(22). However, patients with sinus rhythm constituted only a small proportion of study population. Of the 4 patients with rheumatic mitral stenosis in sinus rhythm, 1 patient developed thromboembolism in this study. The small number of patients in this study makes it difficult to draw definitive conclusions regarding the role of antiplatelet therapy in these patients. A recent case report by Chekhchar and colleagues describes the use of aspirin in a patient with branch retinal artery occlusion and concomitant mitral stenosis in sinus rhythm leading to an improvement in vision and absence of any recurrences(23).

A low dose of aspirin (75 mg) was used in the present study. Since our study was limited to patients with rheumatic mitral stenosis in sinus rhythm without a history of thromboembolic events, a low dose of aspirin was deemed reasonable considering greater rates of bleeding with higher doses(24).

Previous studies of patients with mitral stenosis and sinus rhythm may serve as historical controls to compare the benefits of aspirin in the present study (Table 3). Systemic embolism was demonstrated in 9.1% of patients with mitral stenosis in sinus rhythm over a 3-year follow up by Chiang et al(25).In the same study it was demonstrated that age, presence of a left atrial thrombus, mitral valve area and significant aortic regurgitation were associated with thromboembolism in patients with mitral stenosis in sinus rhythm. This subset of patients may the greatest beneficiaries of antiplatelet therapy given the lack of clear guidelines regarding the use of oral anticoagulation in most of these patients. None of the patients in our study developed cerebral or non-cerebral thromboembolism. There may be several possible explanations for this finding. Patients with rheumatic mitral stenosis and sinus rhythm are at a relatively lower risk of thromboembolism compared to those with atrial fibrillation. Although the lack of any thromboembolic events in the present study may be reflective of the efficacy of antiplatelet therapy with aspirin, the limited follow- up of patients and the fact that a proportion of patients underwent BMV and mitral valve replacement during the study period may also explain our findings. In addition, the fact that only telephonic follow-up was conducted could have been associated with some under-reporting of events.

None of the patients in the present study reported episodes of major or non-major bleeding. The low dose of aspirin used in the present study along with frequent prescription of proton pump inhibitors concomitantly with aspirin may explain this finding.

There are a few limitations of our study. The present study is a single center study thereby limiting its generalizability. However, it is the largest prospective study of rheumatic mitral stenosis patients in sinus rhythm. A significant proportion of patients were non-compliant to aspirin. However, none of these patients reported any major/non-major bleeding episodes or any other significant adverse effects due to the drug. In most cases, the reason for non-compliance of patients to aspirin was the inadvertent advice of their local treating physician. A more frequent follow-up might have ensured better compliance to the drug. Follow-up of patients was limited to 1 year. This may have been insufficient to conclusively determine the efficacy of the drug in view of the low stroke rates in this group of patients. An additional limitation of the present study was the inability to perform extended ECG recording to document subclinical atrial fibrillation.

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In conclusion, aspirin is safe and well tolerated in patients with rheumatic mitral stenosis in normal sinus rhythm. Aspirin seems to be a promising drug in the prevention of systemic thromboembolism in the high-risk subgroup of patients with mitral stenosis in normal sinus rhythm. Large randomized controlled trials are needed to confirm the findings of the present study.

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Figure Legend

Figure 1. Study profile.

N: number of patients; AF: atrial fibrillation; GI: gastrointestinal; mg: milligram.

TABLES

Table 1. Baseline clinical and echocardiographic characteristics of patients (N = 275)

Characteristic	**(mean ± SD) or n (%)**
Age, years	34.8 ± 11.8
Female sex	163 (59)
Functional class NYHA I NYHA II NYHA III NYHA IV	 58 (21) 203 (74) 14 (5) 0 (0)
Mitral valve area, cm^2	0.9 ± 0.3
LA Diameter, mm	42.9 ± 6
Spontaneous echocardiographic contrast	7 (2.5)
Right ventricular systolic pressure, mmHg	41 ± 8
Significant AR	53 (19.3)
Significant MR	60 (21.8)

N: Number of patients enrolled; n: number of patients; %: percentage; SD: standard deviation; LA: left atrium; AR: aortic regurgitation; MR: mitral regurgitation cm: centimetre; mm: millimetre; mmHg: millimetre of mercury.

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Table 2. Reasons for non-compliance to aspirin

Reason	**n (%)**
Cessation of therapy on the recommendation of local general physician	41(62)
Failure to remember taking the drug	13(19)
Cost of the drug	10(15)
Other reasons	3(4)

n: number of patients; %: percentage

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Table 3. Rates of systemic embolism in historical controls (mitral stenosis in sinus rhythm)

Study	**Mean duration of follow- up**	**Stroke/ TIA/ Systemic embolism**
Bannister, 1960(26)	4.5 years	9.1%
Szekely, 1964(13)	20 years	3.8%
Coulshed, 1970(2)	13 years	7.9%
Fleming and Bailey, 1971(27)	9.5 years	11.6%
Chiang et al, 1998(25)	3 years	9.1%
Karthikeyan, 2014(6)	10.2 months	5.3/ 100 patient-years
Present study	8.2 months	0

TIA: transient ischemic attack; %: percentage

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Figure 1. Study profile.