ORIGINAL ARTICLE

RESOLUTION OF LEFT ATRIAL THROMBUS IN SEVERE MITRAL STENOSIS PATIENTS AFTER THREE MONTHS OF ANTICOAGULATION

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Objectives: To determine frequency of LA clot resolution in patients with severe MS after three months of anticoagulation.

Methodology: A descriptive study was conducted over 6 months from Jul 2018 to Jan 2019 including 49 patients who fulfilled the inclusion criteria and visited Cardiology department, NICVD Hospital-Karachi. After clinical evaluation, warfarin therapy was given for 3 months followed by Transesophageal echocardiography (TEE) to access the resolution of LA thrombus. Chi-square test and Fisher Exact test were used to assess the effect of patient characteristics and echocardiographic findings on the resolution of thrombus.

Results: The mean age of the study patients was 47.51±9.93 years. The average mitral valve area (cm2) was observed to be 0.68±0.16, while the average size of left atrial (mm) was 54.38±7.19. At the end of 2 months, TEE showed successful resolution of clot in 11 (22.4%). While by the end of 3 months, only 6 (12.2%) patients showed successful resolution of clot.

Conclusion: After 3 months of oral anticoagulation, the LA thrombus resolved in almost 1/4th of the study patients. Successful clot resolution showed positive correlation with history of stroke, hemoptysis and clot mobility and negative correlation with severity of tricuspid regurgitation.

Keywords: Severe Mitral Stenosis, Left Atrial Thrombus, Transesophageal Echocardiography

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INTRODUCTION

Atrial fibrillation (AF) in the presence of rheumatic mitral stenosis (MS) is linked to an increased risk of thromboembolism. In rheumatic MS, the presence of left atrial (LA) thrombi is a common occurrence.[1] The left atrial appendage (LAA) clot is responsible for most AF-related embolisms.[2] The anatomic configuration of LAA in patients of MS provides a conducive environment for clot formation in individuals with AF.[3] However, the formation of LA thrombus in MS patients and the significant embolic events found in roughly 20% of these individuals cannot be explained by valvular stenosis alone.[4]

MS is the most prevalent long-term consequence of rheumatic fever (RF) in adults, although it can also be congenital in newborns.[5] Development of LA thrombus is common in MS patients, especially those with atrial fibrillation.[6] The altered anatomy and enlarged volume of the left atrium, aberrant flow of blood into the atrium, atrial contraction abnormality, reduced valve area, and poor endothelial function are the main factors of increased thrombus formation risk in these patients.[6] A threefold increase in the likelihood of embolic events is suggested to be linked to LA thrombus.[7] In addition to the severity of MS, investigators have identified a number of other risk factors for LA thrombus, including advanced age, the length of symptoms, a low cardiac output state, and the size of the LA.[8] Contrast-enhanced magnetic resonance imaging (MRI) scans have shown a high sensitivity and specificity for detecting thrombus in LA, still echocardiography remains the best accessible non-invasive technique for detecting it due to its extensive availability and adaptability.[9] The accuracy of transthoracic echocardiography (TTE) is questioned, particularly when a thrombus forms in the LAA, transesophageal echocardiogram (TEE) has

been demonstrated to be more accurate and sensitive in this regard.[9]

According to the literature, the frequency of left atrial thrombi is between 20 and 33%.[6] Moreover, chronic AF affects 50% or more of people with severe symptomatic MS. AF and LA enlargement, both have the ability to change the course of the disease by providing a source of mural thrombi (LA clot) and increasing the risk of systemic embolism.[10] Apart from cerebral embolization, these emboli can cause obstruction of extremity arteries, aortic bifurcation occlusion, and visceral or myocardial infarction.[10]

TEE is an established standard for detecting LA or LAA thrombi.[11] Current guidelines advocate vitamin K antagonist (VKA) treatment with an INR of 2.0 to 3.0 and a follow-up TEE to confirm thrombus resolution.[12] Insufficient anticoagulation may also increase the chances of thromboembolic events. In contrast, prolonged anticoagulation can increase the bleeding chances. Therefore, it is important to understand the optimal duration of anticoagulation in patients having MS for effective resolution of LA clots and minimize the risk of thromboembolic events as well as bleeding. Short-term effects of oral anticoagulation on a thrombus at specified durations are consider much more clinically important for the safer candidacy of patients for any procedural management of the disease. No prior data are available on the short-term effect of anticoagulation in MS patients with LA Clot in our population. With varying dietary habits, medication adherence, and socio-demographic differences, the short-term effect of anticoagulation in our population is expected to differ from that of the western world. Therefore, this study aims to evaluate the short-term (3 months) effect of anticoagulation in the resolution of the left atrial clot in patients with severe mitral stenosis.

METHODOLOGY

A descriptive study was conducted at the National Institute of Cardiovascular Disease (NICVD), Karachi-Pakistan, from 29th Jul 2018 to 29th Jan 2019. Approval of the ethical review committee of NICVD was taken before the data collection. Consecutive forty nine study subjects were recruited. Sample size was calculated based on 95% confidence interval, 7% of absolute precession, and 93.9% of expected prevalence (p), a minimum of n = 45 severe MS patients with a clot in the LAA were required. The involvement of LAA study subjects, in terms of participation in this study, was ensured at all stages. The lead investigator carried out clinical evaluation of participants including evaluation for prior stroke, hemoptysis, NYHA functional class, and cardiac rhythm. Patients of severe MS from both genders with the age range of 18-65 were recruited after the confirmation of diagnosis of LA clot using TEE. All patients had their mitral valve area (cm^2), mitral valve score, LA size (cm), pulmonary artery pressure (mmHg), degree of tricuspid regurgitation (mild, moderate, severe), LA thrombus position, and thrombus mobility (fixed, movable) assessed. After the informed consent, TEE was performed as per the standard settings of the procedure. The demographic profile of the patients was recorded and baseline TEE was interpreted. Parameters such as the mean of mitral valve area (MVO) (cm^2), MPG (mmHg), and LA size (AP diameter, cm) were recorded. Patients were given warfarin at a starting dose of 5 mg per day. Monthly INR monitoring was performed, and dose of warfarin was modified to achieve INR goal range between 2 to 3. After three months of anticoagulation, repeat TEE was carried out to assess the presence or absence of a clot. Data computation and statistical analysis was carried out using SPSS. Chi-square test or Fisher Exact test were used to assess the effect of patient characteristics and echocardiographic findings on the resolution of thrombus.

RESULTS

The descriptive statistics of demographics, clinical parameters and echo findings are presented in Table 1. The mean age of the study patients was 47.51±9.93 years. Out of 49 patients, 32 (65.3%) were males, while 17 (34.7%) were female. The average mitral valve area (cm2) was observed to be 0.68±0.16, while the average size of left atrial (mm) was 54.38±7.19. Almost 24.5% of the study patients had a history of stroke, while 18.4% had a history of hemoptysis. With respect to NYHA class, majority of the patients (53.1%) belong to NYHA III Class, while the least (10.2%) belong to I and IV Class (Table 1).

Table 1: Socio-demographic characteristics of the study participants

	Summary
Total (N)	**49**
Age (years)	47.51 ± 9.93
Gender	
Males	32 (65.3%)
Females	17 (34.7%)
Mitral valve area (cm^2)	0.68 ± 0.16
Wilkins score	8.24 ± 0.92
Left atrial size (mm)	54.38 ± 7.19
International Normalized Ratio (INR)	
At 1 month	2.81 ± 0.55
At 2 months	2.76 ± 0.32
At 3 months	2.89 ± 0.41
History of stroke	12 (24.5%)
History of hemoptysis	9 (18.4%)
New York Heart Association (NYHA) Class	
I	5 (10.2%)

II	26 (53.1%)
III	13 (26.5%)
IV	5 (10.2%)
Rhythm	
Atrial fibrillation	32 (65.3%)
Sinus rhythm	17 (34.7%)
Mildly raised	17 (14.3%)
Pulmonary artery pressure (PAP)	
Moderately raised	24 (49%)
Severely raised	18 (36.7%)
Mild	12 (24.5%)
Tricuspid regurgitation	
Moderate	19 (38.8%)
Severe	18 (36.7%)
Left Atrial (LA) thrombus position	
Left Atrial Appendage	24 (49%)
Left Atrial Cavity	25 (51%)
Mobility of thrombus	
Fixed	32 (65.3%)
Mobile	17 (34.7%)

The values represented in Table 1 are mean and SD, for age, gender, Mitral valve area (cm^2) and INR. While the NYHA class, Rhythm, PAP, Tricuspid regurgitation, LA thrombus position and mobility of thrombus in the study are represented by frequency and percentage.

The warfarin dose adjustments at monthly follow-ups are demonstrated in Table 2. Majority of the patients did not require dose modification from 5mg starting dose. At the end of 2 months, TEE showed successful resolution of clot in 11 (22.4%). While by the end of 3 months, only 6 (12.2%) patients showed successful resolution of clot (Table 2).

Table 2: Dose Adjustments (Warfarin Therapy) over the course of three months

Warfarin Therapy	Dose adjusted		Dose not adjusted
	Reduced to 2.5 mg	Increased to 7.5 mg	
1st Month	7 (14.3%)	4 (8.2%)	38 (77.6%)
2nd Month	11 (22.4%)	2 (4.1%)	36 (73.5%)
3rd Month	6 (12.2%)	2 (4.1%)	41 (83.7%)

Values are frequency and percentage and are representing the dose adjustment data of the study, with different doses.

Successful clot resolution showed positive correlation with history of stroke ($p = 0.001$), hemoptysis ($p < 0.001$), clot mobility ($p = 0.003$) and negative correlation with severity of tricuspid regurgitation ($p= 0.028$). The associations of thrombus with other parameters, including Rhythm, thrombus mobility was not statistically significant. While the NYHA functional class and the thrombus area were shown to be significant (Table 3).

Table 3: Resolution of left atrial thrombus and its association with patient characteristics and echocardiographic findings

	Resolution of Left Atrial Thrombus		P-value
	Resolved	Unresolved	
Total (N)	**11**	**38**	
Age group			
18 to 40 years	4 (25%)	12 (75%)	0.635
41 to 65 years	7 (21.2%)	26 (78.8%)	
Gender			
Male	8 (25%)	24 (75%)	0.084
Female	3 (17.6%)	14 (82.4%)	
History of stroke			
Yes	7 (58.3%)	5 (41.7%)	0.001*
No	4 (10.8%)	33 (89.2%)	
History of hemoptysis			
Yes	6 (66.7%)	3 (33.3%)	0.000*
No	5 (12.5%)	35 (87.5%)	
NYHA class			
I – 11	7 (22.6%)	24 (77.4%)	0.622
III – IV	4 (22.2%)	14 (77.8%)	
Rhythm			
Atrial fibrillation	6 (18.8%)	26 (81.3%)	0.395
Sinus rhythm	5 (29.4%)	12 (70.6%)	
Mitral valve area (cm2)			
0.1 - 0.5	3 (25%)	9 (75%)	0.688
0.51 - 0.99	8 (21.6%)	29 (78.4%)	
Mitral valve score			
4 – 6	1 (50%)	1 (50%)	0.415
7 – 10	10 (21.3%)	37 (78.7%)	
Left atrial size (mm)			
41 – 55	6 (18.8%)	26 (81.3%)	0.16
56 – 70	5 (29.4%)	12 (70.6%)	
Pulmonary Artery Pressure			
Mildly raised	2 (28.6%)	5 (71.4%)	0.35
Moderately raised	7 (29.2%)	17 (70.8%)	
Severely raised	2 (11.1%)	16 (88.9%)	
Tricuspid regurgitation			
Mild	6 (50%)	6 (50%)	0.028*
Moderate	2 (10.5%)	17 (89.5%)	
Severe	3 (16.7%)	15 (83.3%)	
LA Thrombus Position			
Left Atrial Appendage	6 (25%)	18 (75%)	0.675
Left Atrial Cavity	5 (20%)	20 (80%)	
Mobility of thrombus			
Fixed	3 (9.4%)	29 (90.6%)	0.003*
Mobile	8 (47.1%)	9 (52.9%)	

**p-value<0.05 is considered significant*
The Demographic & Clinical Characteristics, along with Transthoracic echocardiographic findings and Transesophageal echocardiography index are represented in frequency and percentages using statistical software SPSS.

DISCUSSION

Though some investigators have urged immediate surgical removal of LAA as the ultimate treatment option due to the potentially complications of anticoagulation therapy and uncertain efficany,[13] successful management with anticoagulant therapy has been documented in patients who are not amenable to surgery.[14] PTMC after complete clearance of LAA thrombus with oral anticoagulation minimizes the chances of thromboembolic events.[15,16] Although thrombus clearance has been reported with long-term oral anticoagulation,[17-23] the clinically significant consequence of short-term anticoagulation has not being documented earlier and is not well established.

In our study, the INR within the target range of 2-3 lead to thrombus resolution in 22.4% of patients. Silaruks et al, in his study suggest that only 2.7% of patients with a mean INR less than 2.5 experienced thrombus clearance.[24] In fact, no thrombus resolution occurred in patients with a mean INR of less than 2.44 in the first six months or in case of a thrombus area more than 2.11 cm.[2,20] Similarly, a study was conducted to evaluate the efficacy of anticoagulation in resolving LA clot in patients with atrial fibrillation. TEE showed complete resolution of clot in 80.1% of patients after 47±18 days of anticoagulation, and 85.1% resolution after 107±21 days.[25] However, the proportion of patients with pure mitral stenosis was only 10.3% in this study. Silaruks S et al. found that after 6 months of oral anticoagulation, roughly a quarter (24.2%) of percutaneous transvenous mitral commissurotomy (PTMC) candidates had their left atrial thrombus vanish on TEE assessment.[24] Thrombus resolution was predicted by a reduced clinical severity, a lower grade of the left atrial spontaneous echocardiographic contrast, a smaller thrombus, and a higher INR level.[20]

We chose the first three months after starting oral anticoagulation to investigate a short-term effect and considered the highest therapeutic importance, based on previous research and also for patient convenience.[17-23] Our results suggest that a shorter duration would have been ineffective, and a longer duration would have had increase the chances of systemic embolism.

The NYHA functional class and the thrombus area were shown to be significant. Independent predictors for thrombus resolution before prescription of oral anticoagulation in the study NYHA class I-II, Left Atrial Appendage position, and mobile thrombus predict thrombus resolution. When compared to study by Silaruks et al, the NYHA functional class and the thrombus area were shown to be significant, and independent predictors.[24] In comparison to Silaruks et al.[24], INR in the range of 2-3 predicts thrombus resolution in our study. Results of our study emphasizes the impact of initial thrombus area on thrombus resolution and the need to maintain an INR of 2.5 or higher to improve thrombus resolution after starting oral anticoagulant therapy.

With successful results, our study also has certain limitations. A major limitation of our study was its inability to assess the potential impact of various LAA morphologies on clot resolution. Getting this information could be very helpful in directing patients with LAA clot directly for surgery rather than delaying it in a hope for clot dissolution.

CONCLUSION

After three months of oral anticoagulation, the left atrial thrombus resolved in almost 1/4th of the candidates. Successful clot resolution showed positive correlation in patients with a history of stroke, hemoptysis, and clot mobility, while a negative correlation was observed with the severity of tricuspid regurgitation. The associations of thrombus with other parameters, including Rhythm, thrombus mobility was not statistically significant. While the NYHA functional class and the thrombus area were shown to be significant.

AUTHORS' CONTRIBUTION

FA and KFA: Concept and design, data acquisition, interpretation, drafting, final approval, and agree to be accountable for all aspects of the work. AN, RG, MUH, PA, SYH, SM, FAT, IR, and TA: Data acquisition, interpretation, drafting, final approval and agree to be accountable for all aspects of the work.

Conflict of interest: Authors declared no conflict of interest.

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