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KEY WORDS:

RHEUMATIC MITRAL STENOSIS WITH LEFT ATRIAL APPENDAGE THROMBUS – EFFECT OF ORAL ANTICOAGULATION ON LEFT ATRIAL APPENDAGE THROMBUS RESOLUTION

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ABSTRACT

Aim: Rheumatic heart disease is one of the commonest cardiac condition in India in both children and adults. Left atrial (LA) thrombus formation remains a significant problem causing morbidity and mortality in rheumatic mitral stenosis. This study is aimed to study the effect of oral anticoagulation on resolution of left atrial appendage thrombus.

Methods: Thirty patients with severe mitral stenosis who showed evidence of left atrial appendage thrombus by transoesophageal echocardiography and who gave consent for the study were selected for the study. Five patients who lost follow-up were excluded from the study.The dose of Acitrom needed ranged between 2 to 4 mg / daily, and all patients were maintained with INR 2 to 3 over a mean period of 6 weeks.

Results: This study involved twenty-five patients (16- female; 9- male) aged between 22 to 44 years (Mean 32.2 +_6.4 years).All the patients had severe mitral stenosis with mean mitral valve area by pressure half time method was 0.62 +_0.11 sq.cm and mean and peak gradient 15.4+_1.95 and 24.65 +_2.98 mm Hg.LA appendage was dilated in all patients with maximum area by planimetry method ranged between 3.8 cm 2 to 7.35 cm 2, mean+_ SD (5.32 +_0.77 cm2).LA appendage thrombus was present in all patients. Their major and minor dimensions ranged between 1.2x1.1 cm to 4.7 x 2.1 cm.The dose of Acitrom needed ranged between 2 to 4 mg / daily, and all patients were maintained with INR 2 to 3 over a mean period of 6 weeks.Focussed TEE done at 6th week showed complete resolution of LA appendage thrombus resolved in four patients and more than 30% reduction in size of thrombus in four patients. In the remaining 17 patients there were no significant changes in the size of the thrombus. None of the patients showed significant increase in size of the thrombus. Repeat objective reassessment of left atrial spontaneous echo-contrast was done. None of the patients showed any notable change in grade of LASEC.

INTRODUCTION

Rheumatic heart disease is one of the commonest cardiac condition in India in both children and adults, accounting for 10-15 % of cardiac cases admitted in hospital. Approximately 25% of all patients with rheumatic heart disease have pure or predominant mitral stenosis (MS).Thromboembolism develops in at least 20% of mitral stenosis patients, at some point of time during the course of their disease.

Thromboembolism remains an important cause of morbidity and mortality in rheumatic MS.Deverallet al.(1) reported that 16% of patients evaluated for MS had a history of systemicembolism. Rowe et al(2), found that 19% of 110 deaths in the first 10 years of follow-up are due tosystemic embolism.

Cardiogenic embolism in mitral stenosis is most often due to left atrial (LA) thrombi and at times due to mitral valve vegetation. Left atrial appendage (LAA) is the commonest site from where the thrombus originates.In the follow-up series of Olesen(3), 22% of all deaths in MS were due to thromboembolism.In the classical series of Coulshed et al(4), 737 patients with predominant mitral stenosis werefollowed up for cardiac events.

Echocardiography is the widely used method for detecting left atrial and left atrial appendage thrombi. Transthoracic echocardiography (TTE) is only 50% sensitive in detecting LA and LAA thrombi. Transesophageal echocardiography (TEE) is superior to TTE and is 99% sensitive and specific in detecting LA and LAA thrombi.

Left atrial dimensions were measured in end systole in PLAX-antero posterior (D1)and two orthogonal diameters in four chamber view (D2 & D3) and left atrial volume calculated by using prolate ellipse method.

Left atrial volume = (D1 X D2 X D3) X 0.523

In patients with MS in SR, LA size correlates with the development of AF, and it is recommended by ACC and AHA guidelines that those with LA size greater than 5.5 cm can be prophylactically anticoagulated.

Madden et al(5), first proposed that increased left atrial size is associated with increased risk of systemic embolism, which was supported by Sommerville and Chambers(6), who reported a threefold increase in embolism in patients with mitral stenosis with enlarged left atrial appendage on chest X-ray compared with those who did not. These observations were not supported by subsequent studies,including a multifactorial study by Peterson et al(7).

Patterns of pulmonary venous Doppler flow are complex and is best visualised by TEE.Keran et al(8) in 1990, analysed pulmonary venous flow in MS by TTE. In mild to moderate MS, the systolic (S) wave was more prominent. The diastolic (D) wave, wascontinuous throughout to end of diastole, with a low flow shape and reduced peak velocity

Left atrial spontaneous echo contrast (LASEC) or "Smoke" occurs in conditions that favours stasis of blood .It is associated with an increased risk of LA thrombus formation and arterial embolization and is better identified by TEE. Medical treatment for LA and LAA thrombus in rheumatic MS is still unclear.

Several studies indicate that adequate anticoagulation using oral anticoagulants in those with atrial fibrillation and in those with documented thrombus reduce the frequency of thromboembolic phenomena. However there are not enough data whether anticoagulation resolves or reduces size of LA thrombus in patients

with rheumatic MS, and thus simplifying hence simplifying surgical or interventional treatment for diseased valves otherwise suitable for closed mitral comissurotomy (CMC)or balloon mitral valvotomy (BMV).

Current study is aimed

1. To study the effect of oral anticoagulation on resolution of left atrial appendage thrombus.
2. To analyse various factors associated with resolution or reduction in size ofleft atrial appendage thrombus.
3. To analyse effect of oral anticoagulation on left atrial spontaneous echo contrast.

METHODS

This prospective study was performed in the year 2005 in the Department of Cardiology, Madras Medical College and Government General Hospital, Chennai.

INCLUSION CRITERIA

1. Patients with severe isolated mitral stenosis with valve anatomy suitable for PTMC/CMC
2. No significant lesions in other valves (mild or less only selected) except for Tricuspid regurgitation secondary to Pulmonary hypertension.
3. NYHA Class I-III status.
4. Patients newly started oral anticoagulation, with no significant oral anticoagulation previously.

EXCLUSION CRITERIA

1. Patients with NYHA class IV status.
2. Moderate to severe calcification of mitral valve
3. Left atrial body thrombus.
4. Significant other valve involvement (more than mild) including significant mitral regurgitation.
5. Significant co-morbid conditions.
6. Previous cardiac surgery including closed mitral commissurotomy.
7. Pregnancy and puerperium.
8. Those patients who did not give consent

Thirty patients with severe mitral stenosis who showed evidence of left atrial appendage thrombus by transoesophageal echocardiography and who gave consent for the study were selected for the study. Five patients who lost follow-up were excluded from the study.

Informed consent was obtained from all the patients after explaining the study.

A thorough history including NYHA status of breathlessness, orthopnoea, PND, H/O thromboembolism, peripheral oedema, chest pain, palpitations, haemoptysis and previous treatment details were obtained.Complete physical examination was done in all patients. A 12 lead electrocardiogram and chestX-ray were taken routinely. Repeat ECGs were taken as and when needed.

The study group included 25 patients (16 female and 9 male) aged between 22 to 44 years (mean32.2 yrs).All patients had definite evidence of left atrial appendage thrombus by TEE.20 patients were in atrial fibrillation (including 3 patients in intermittent atrial fibrillation) and 5 patients were in sinus rhythm during the study.The dose of Acitrom needed ranged between 2 to 4 mg / daily, and all patients were maintainedwith INR 2 to 3 over a mean period of 3 weeks.

ECHOCARDIOGRAPHIC DATA

A complete Transthoracic echocardiogram was obtained including M- mode, 2D, colour Doppler and pulse& continuous wave Doppler in every patient.ALOKA Trivitron model echo machine was used for this study. A 2.5 MHZ probe was used for transthoracic echocardiography and a 5 MHZ multiplane probe was used for transesophageal echocardiography.

Lesion severity in individual valve was characterised by various methods.

Specific attention was paid in assessing mitral valve morphology, Wilkin's scoring, mitral valvearea by planimetry & pressure half time method, peak and mean trans mitral gradient.M-mode echocardiogram with cube formula was used to assess global LV systolic function. M-modeechocardiogram at mitral & aortic valve level was obtained routinely for measurement.

Left atrial appendage function was assessed using pulsed Doppler imaging, with sample volume positoned at mouth of the appendage; the maximal velocity during atrial contraction was measured.This velocity corresponds to the force of atrial appendage contraction or emptying.

Pulmonary venous pulsed wave Doppler was obtained from left upper lobe pulmonary vein. Entire leftatrium was searched for thrombus and specific note was made on mitral valve morphology and leftatrial spontaneous echo contrast.

All patients received standard medical treatment with, Digoxin, Penicillin, Pottasium chloridesyrup, Verapamil, Diuretics and other drugs according to the clinical condition.Oral anticoagulation started in all patients with 2 -3 mg of Acitrom(Acenocoumorol) once daily.Dose adjustments were made weekly by monitoring Prothrombin time and INR (Internationalnormalised ratio).

INR was maintained between 2-3. Patients were followed up weekly by monitoring anysymptom change, bleeding, thromboembolic episode, and prothrombin time and INR measured. FreshECGs were taken when clinical suspicion of change in rhythm was noted.Oral anticoagulation was continued for 6 weeks

Focussed transthoracic and transesophageal echocardiogram was repeated after 6 weeks and theimportant parameters were collected. Left atrial appendage thrombus presence/absence, and if LAAthrombus was present, its size in major and minor dimensions were measured in both TTE and TEE.A note on LA spontaneous echocontrast was made.

All the data collected were subjected to statistical analysis and conclusion derived.

OBSERVATIONS

This study involved twenty five patients (16- female; 9- male) aged between 22 to 44 years(Mean 32.2+_ 6.4 years).Among these patients 17 patients were in atrial fibrillation and 5 patientsremained in sinus rhythm throughout the study. Three patients who were in AF during start of the study

showed intermittent sinus rhythm during follow-up.

All the patients had severe mitral stenosis with mean mitral valve area by pressure half timemethod was 0.62 +_ 0.11 sq.cm and mean and peak gradient 15.4+_1.95 and 24.65 +_ 2.98 mm Hg. Mitral regurgitation was mild in 14 patients and trivial in 11 patients.

None of the patients had significant aortic valve disease (3-patients had mild aortic stenosis and8-patients had mild aortic regurgitation).None of the patients had significant tricuspid stenosis. Tricuspid regurgitation secondary to pulmonary hypertension was present in all patients .7 patients had severe TR, 5 patients had moderate TR and remaining 13 patients had mild TR. Pulmonary hypertension secondary to mitral stenosis was severe in 10 patients and moderate in 12 patients andmild in 3 patients.

The Wilkin's score ranged between 5 to 9 with Mean +_ SD was 7.32+_1.1. Left atrial dimension inparasternal long axis at aortic valve level was 5.86 +_0.56 cm. LA volume calculated by prolate ellipsemethod was 151.05 +_40.27 ml.

All patients showed evidence of left atrial spontaneous echo-contrast (LASEC).Eleven patients were graded to have Mild LASEC and fourteen patients had ble change in the marked LASEC. LA

appendage was dilated in all patients with maximum area by planimetry method ranged between 3.8 cm2 to 7.35 cm 2, mean+_ SD (5.32 +_0.77 cm2).Average LA appendage ejection fraction was 19.20+_8.4 % in the study group and markedly differed between sinus rhythm group and atrial fibrillation group.

In sinus rhythm LAA ejectionfraction was 31.52+_ 7.9 % and in those with AF it was 16.1+_5.13%. LA appendage emptying velocity ranged between 7 cm /sec to 50 cm/sec with mean +_ SD 17.9+_ 11.7 cm/sec, which also differed significantly between two groups .In atrial fibrillation group LAA-EF was 12.63+_4.95 cm/sec and insinus rhythm group it was 39 +_ 2.6 cm/sec.LA appendage thrombus was present in all patients. Their major and minor dimensions ranged between 1.2x1.1 cm to 4.7 x 2.1 cm.

The dose of Acitrom needed ranged between 2 to 4 mg / daily, and all patients were maintained with INR 2 to 3 over a mean period of 3 weeks. None of the patients reported significant symptomchange or any history suggestive of thromboembolic episode during 6 weeks follow-up .On serial ECGs3 patients showed sinus rhythm intermittently. All of them were in atrial fibrillation on 6th week .

Focussed TEE done at 6th week showed complete resolution of LA appendage thrombusresolved in four patients and more than 30% reduction in size of thrombus in four patients. In theremaining 17 patients there were no significant changes in the size of the thrombus. None of the patients showed significant increase in size of the thrombus. Repeat objective reassessment of left atrial spontaneous echo-contrast was done. None of the patients showed any notagrade of LASEC.

RESULTS

Resolution of Left atrial appendage thrombus occurred in 16% (4) of the individuals. Reduction in size of more than 30%was seen in 16% (4) patients.Remaining 68% (17) of the patients showed no significant change in thrombus size. None of thepatients showed significant symptom change or thromboembolic episode or any bleeding. No significant change in grading of LASEC was noted in any of the patients.

RESULTS

	Age(yrs)			Rhythm			Clot Size(major dimension)		LAA Emptying Velocity	
	<30 (6)	30-40 (15)	>40 (4)	AF (17)	AF-I (3)	SR (5)	<1.5cm (10)	>1.5cm (15)	<30 cm/s (19)	>30 cm/s (6)
Resolution	(2) 33.3%	(2) 13.3%	(0)	(1) 5.8%	(1) 33.3 %	(2) 40%	(4) 40%	(0)	(0)	(4) 66.6%
>30% Size Reduction	(2) 33.3%	(2) 13.3%	(0)	(1) 5.8%	(1) 33.3%	(2) 40%	(2) 20%	(2) 13.3%	(2) 10%	(2) 33.4%
No / Minimal Change	(2) 33.3%	(11) 73.3%	(4) 100%	(15) 88.4%	(1) 33.3%	(1) 20%	(4) 40%	(13) 86.7%	(17) 90%	0

SUB GROUP ANALYSIS

LAA thrombus resolution or reduction in size occurred in 66.6% of patients in the age group of <30 years and in 26.6% of patients in the age group of 30 to 40 years. None of the patients above 40 years of age had any resolution or reduction in size of the thrombus. The mean age of patients who showed complete resolution was 27.25 years as against 34.05 years in patients with no resolution.

Similarly 60% of patients in sinus rhythm and 66.6 % of patients with intermittent AF showed resolution or reduction in size of the study. But only 11.6%of patients with atrial fibrillation showed resolution or reduction in size and 88.4% of patients withatrial fibrillation showed no or minimal change in thrombus size.

All the patients who showed complete thrombus resolution had thrombus dimension less than1.5 cm in major axis. Among the patients with thrombus dimensions > 1.5 cm size, none of themshowed complete resolution and only 13.3% showed significant reduction in size.

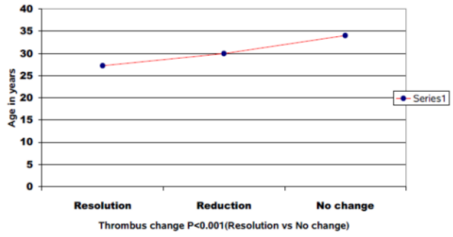
There is no significant difference in mitral valve area among the three groups. Mean Wilkin's score wassignificantly lower in patients who had thrombus resolution as against those without resolution (6.5 vs 7.47).Patients showing no change in thrombus dimension had significantly higher left atrial dimensionsand volume.

Patients who showed resolution of thrombus had significantly higher LAA ejection fraction compared with those showing no change in thrombus dimensions. (28 +_ 0.12 vs15.86 +_ 0. 06)Similarly patients who had resolution of thrombus had significantly higher LAA peak emptying velocity compared with those without any change. (32.5 +_ 14.1 cm/sec. vs 12.45 +_5.96 cm/sec.)

SUB GROUP ANALYSIS

Characteristics	Resolution	Reduction	No change	P value (Resolution vs No change)
Age(Yrs)	27.25±6.4	30±7.6	34.05±5.6	< 0.001
Sex				
Male	2	1	6	0.1
Female	2	4	10	NS
Rhythm				SR vs AF
SR	2	2	1	
AF	1	1	15	<0.0001
AF-I	1	1	1	
Wilkins's score	6.5±1	7.5±1.29	7.47±1.06	<0.01
LA dimension(cm)	5.67±0.68	5.6±0.59	5.97±0.52	<0.01
LA volume(ml)	138.95±56.2	146.25±26.0	155.05±39.9	<0.02
LAA-EF(%)	28±0.12	24.93±0.05	15.86±0.06	<0.001
LAA empt. Vel.(cm/sec)	32.5±14.1	26.5±14.66	12.45±5.96	<0.001
Mitral valve area	0.63±0.12	0.60±0.12	0.62±0.1	0.5 NS
Thrombus size				<0.0001
Less than 1.5 cm	4	2	4	
More than 1.5 cm	0	2	13	

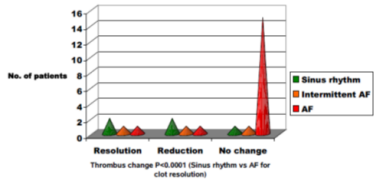
AGE



Thrombus change P<0.001(Resolution vs No change)

The chance of clot resolution reduces with age

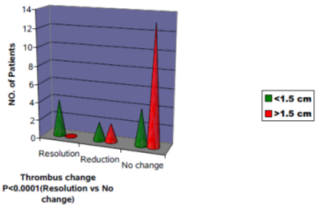
RHYTHM



Thrombus change P<0.0001 (Sinus rhythm vs AF for clot resolution)

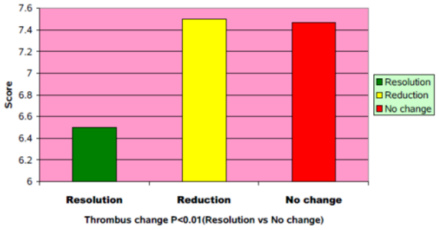
Sinus rhythm favours thrombus resolution, whereas persistant AF is associated with poor resolution

THROMBUS SIZE



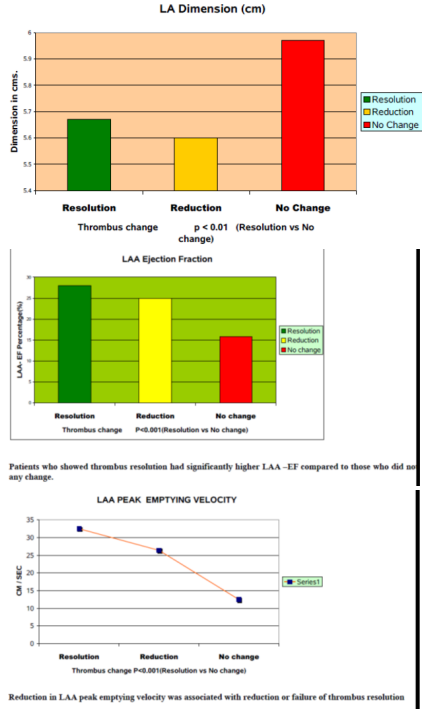
Thrombus size significantly influences resolution. Those with < 1.5 cm size resolves rapidly as against those with size > 1.5 cm, which were associated with poor resolution

WILKIN'S SCORE



Thrombus change P<0.01(Resolution vs No change)

Higher Wilkin's score is associated with lower clot resolution



DISCUSSION

Anticoagulation is conventionally used to reduce the risk of the thromboembolic events associated with AF. Oral anticoagulants act by inhibiting the synthesis of vitamin K-dependent coagulation factors. This prevents new thrombus formation, and promotes adherence and organizationof old thrombi to the surrounding endocardium.

However, recent studies have supported an alternative hypothesis of benefit that includes not only the prevention of new thrombus formation but also the resolution of existing thrombi.In situations in which a thrombus is already present, anticoagulation prevents further thrombus extension, thereby facilitating the action of endogenous fibrinolysis.

A study conducted by Kandpal et al. showed that 41.7% of isolated LA appendage clotsresolved in contrast to 12.5% of LA body clots in patients with mitral stenosis after 6 months of oralanticoagulation. Resolution of atrial thrombi after oral anticoagulation in patients with non- valvular
AF has also been examined in several studies.

In the present study, we have analyzed factors associated with resolution of LA appendagethrombus with oral anticoagulation. Older age (>40 years) was not only associated with increased prevalence of left atrial thrombus but alsowith failure of thrombus resolution with anticoagulation.

Similarly presence of atrial fibrillation favors stasis and abnormal low velocity flow patterns in the leftatrium and appendage associated with failure of thrombus resolution. Left atrial appendage peak emptying velocity and LAA ejection fraction were significantly lower in patients with atrial fibrillationand are associated with failure of thrombus resolution.

On the other hand patients with sinus rhythm had significantly higher LAA peak emptying velocity andLAA ejection fraction and associated with better resolution or reduction in thrombus size.From the above observations it seems prudent that intact mechanical function of left atrial appendage facilitates the action of oral anticoagulants on the thrombus and resulting in resolution.

Patients with smaller thrombus size (<1.5 cm) showed better resolution compared with larger thrombus size. This difference is possibly explained by the fact that a higher thrombus burden does not permit dissolution with endogenous fibrinolysis despite optimal anticoagulation and with much smallerthrombus burden, allows dissolution by endogenous fibrinolysis, while effective oral anticoagulationprevents fresh thrombus formation.

From the above observations a management strategy can be derived. Stable patients withisolated severe mitral stenosis whose valve anatomy is suitable for balloon mitral valvulotomy withisolated left atrial appendage thrombus can afford to be on adequate oral anticoagulation for a short period (6weeks to 6 months) if the thrombus is small especially if they are young and in sinus rhythm.

If repeat TEE revealed thrombus resolution they can be subjected to balloon mitral valvotomy or closedmitral commissurotomy.

If the thrombus does not resolve they can be referred for open surgical procedure.On the other hand, older patients and those with large LA appendage thrombus or LA body thrombuscan be straightaway referred for open surgical procedure with clot removal.

Hence it seems prudent that in patients with valve anatomy suitable for BMV /CMC, atrial of oral anticoagulation may be initiated if patient is not overtly symptomatic, and look forclot resolution. If clot resolution is confirmed by TEE, these patients may be benefited byperforming low risk BMV or CMC.

Only few studies(9-13) available regarding this issue .Most of the studies conclude that LA bodythrombus resolution is poor and most patients need open procedure.

CONCLUSION

Adequate oral anticoagulation (INR 2-3) is effective in resolution of left atrial appendage thrombus in rheumatic mitral stenosis in a significant group of patients over a period of six weeks. The resolution is either complete or partial.

Among patients receiving oral anticoagulation, 16% showed complete resolution of thrombus and another 16% showed more than 30% reduction in size of thrombus.

Factors associated with resolution or reduction in size include
Younger age (<40 years)
Small thrombus size (< 1.5 cm)
Sinus rhythm, Intermittent atrial fibrillation

Left atrial appendage peak emptying velocity more than 30 cm/sec.

None of the patients showed significant (>30%) increase in size of the thrombus during the study period.

Factors associated with failure of resolution or reduction in size include

Older age (> 40 years)
Large initial thrombus size (> 1.5 cm)
Persistent atrial fibrillation
Left atrial appendage peak emptying velocity less than 30 cm/sec
Larger left atrial dimensions and volume.

None of the patients showed evidence of thromboembolic events or any bleeding complications during the study period.
Oral anticoagulation did not show any notable change in spontaneous echo contrast in left atrium during the study period.

IMPLICATIONS OF THE STUDY

Patients with rheumatic mitral stenosis with left atrial appendage thrombus who have valve morphology suitable for balloon mitral valvotomy or closed mitral commissurotomy can be subjected to adequate oral anticoagulation for thrombus resolution for a short period (6 to 8 weeks) if they are clinically stable. This is especially so if the patients are young, with smaller thrombus size, particularly if they are in sinus rhythm.

If the thrombus resolves, management is simplified by doing balloon mitral valvotomy or closed mitral commissurotomy, instead of open mitral valvotomy with thrombus removal in those patients.

On the other hand older patients with large left atrial appendage thrombus can be straightaway referred for open surgery especially if they are in atrial fibrillation and low left atrial appendage emptyingvelocity.

LIMITATIONS OF THE STUDY

This is a small non randomised study involving small number of selected patient group. The patient groups are treated for shorter period of time. Further, large-scale study with longer duration (6months) of follow up may be necessary to confirm the findings of our study.

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