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TENECTAPLASE FOR LEFT SIDED PROSTHETIC VALVE THROMBOSIS: A SIX MONTHS FOLLOW UP

Cardiology

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ABSTRACT

Background Thrombosis is a serious and life threatening complication following cardiac valve replacement and is a common cause of referral to the higher centre for intervention. Although surgery has been described as the traditional choice of therapy for the PVT all over the world, thrombolytic therapy is a promising alternative to valve re-operation in PVT. **Methods** Twelve consecutive patients (6 males, 6 females) (2 AVR, 9 MVR and 1 DVR) were included in the study from January 2020 to January 2021. Mean age was 29±10 years. Diagnosis is confirmed both by TTE and fluoroscopy. Mean gradient of patients with mitral PVT were 24.4±4.86mmhg and for aortic PVT was 43.3±13.1mhg. All patients were on Acenocumarol treatment. Average INR on presentation was 1.79±0.34 and 2.53±1.31 for aortic and mitral PVT. Thrombus burden was measured in all patients by TEE. Tenecteplase is given at a dose of 0.5mg/ kg bolus (followed by heparin ACT guided) with clinical and Echocardiographic examinations repeated at 6 and 24 hours after starting thrombolytic therapy. Doppler echocardiography was the primary method to follow for response to therapy at 6 months follow up. **Results** Thrombolytic therapy was successful in all the patients. Mean gradient significantly reduced to 10.3±3.4mmhg and 5.7±3.1mmhg (p=0.001) at 6 and 24 hours for mitral valve and 8.2±4.6mmhg and 5.8±2.5mmhg(p=0.001) for aortic valve. Seven (58.3%) had normal bileaflet movement and 5 (42.7%) had abnormal leaflet movement on fluoroscopy. Two patients had CVA (infarct) and 1 had large sheath site hematoma. None of the patients expired after treatment. At 6 months follow up, Mean gradient were 8.3±2.8mmhg and 10.3±4.72mmhg for mitral and aortic valve. All patients were asymptomatic with no complications. **Conclusion** Our study demonstrates that Tenectaplase is a safe, feasible and effective thrombolytic treatment for patients with PVT and should be considered as first line therapy for prosthetic heart valve thrombosis.

KEYWORDS

INTRODUCTION

With high prevalence of rheumatic heart disease, there are large numbers of patients in India undergoing cardiac valve replacement. Prosthetic valves thrombosis (PVT) is defined as any obstruction of the prosthesis by non-infective thrombotic material. The diagnosis of PVT is made by a combination of clinical data (heart failure, absence of prosthetic sounds, cardiogenic shock) and echocardiograpy. It is a serious complication of mechanical prosthetic valves, as it may lead to life threatening peripheral thromboembolism. The risk of embolism is greater with the valve in mitral position as compared to aortic position. Inadequate thromboprophylaxis due to interruption in oral anticoagulant therapy or recent episodes of atrial fibrillation are important causes of PVT.[1,2] Although surgery has been described as the traditional method of choice for PVT, thrombolytics have been used successfully in the past for the resolution of PVT. Thrombolytic therapy has shown high success rates with low rate of complications and mortality especially in patients with low clot burden (<0.8 cm2) and no history of stroke. Further, use of thrombolytics does not preclude the option of surgery in the event of failure.[3] streptokinase, urokinase and rTPA were in use since long time. Tenecteplase is a new generation thrombolytic with higher fibrin specificity, greater resistance to plasminogen activator inhibitor – I (PAI–I) and longer half life, thus can be given as a convenient single intravenous bolus injection[4]

Table 1: Summary of 12 patients with prosthetic valve thromboosis

No	age	sex	Valve	valve type (mm)	thrombus size (TEE)	NYHA Class	symptoms	INR	TNK dose (mg)
1	30	M	Aortic	SJ BL	15 x 13	III	Dyspnea	1.9	30
2	22	F	Aortic	SJ BL	8X9	IV	Dyspnea	1.8	25
3	30	F	Aortic	SJ BL	9X10	III	Dyspnea	1.4	20
4	22	M	Mitral	SJ BL	12 X14	III	Dyspnea	4.8	35
5	35	F	Mitral	SJ BL	11 X 13	IV	Dyspnea	1.7	40
6	18	M	Mitral	SJ BL	7 X 4	III	Dyspnea	1.6	35
7	36	F	Mitral	SJ BL	9 X 10	III	Dyspnea	3.8	25
8	42	M	Mitral	SJ BL	12 X 14	IV	Dyspnea	4.5	30
9	36	F	Mitral	SJ BL	9 X 6	III	Dyspnea	1.7	35
10	35	M	Mitral	SJ BL	11 X 13	IV	Dyspnea	2.35	30
11	31	M	Mitral	SJ BL	7 X 9	III	Dyspnea	1.8	30
12	40	F	Mitral	SJ BL	10 X 13	III	Dyspnea	1.2	32

Table 2:

No	PG	Mean gradient(mmhg)				TR	RVSP		Complications
		Before	6hrs	24hrs	6months		Before	After	
1	46	30	10	4	5	Mild	64	54	large sheath Site hematoma
2	74	44	18	8	12	Mod	38	34	Nil
3	85	56	24	9	14	No	-	-	Nil
4	41	32	12	3	4	Mild	68	44	CVA
5	38	28	10	7	7	Severe	120	64	CVA
6	28	19	5	5	7	Mod	64	54	Nil
7	38	22	6	6	9	Severe	68	50	Nil
8	30	22	10	5	10	Mild	54	32	Nil
9	47	30	19	12	14	Severe	78	64	Nil
10	30	18	9	6	6	Mild	48	38	Nil
11	38	25	11	5	5	Mild	42	39	Nil
12	32	22	10	4	5	Severe	74	64	Nil

METHODS

The study group included 12 consecuative symptomatic patients with mechanical heart valves (6 male, 6 female; mean age 30.1±7.4years) who underwent thrombolytic treatment between January 2020 to January 2021 in our Department. All patients were considered for treatment on the basis of clinical features and diagnosis was confirmed in all the patients by transthoracic echocardiography and leaflet movement was confirmed by fluoroscopy.

The TEE was performed using 12-MHz multiplane transducer connected to a system (Vingmed CFM 800) after oropharyngeal anesthesia (2% lidocaine) and conscious sedation (intravenous midazolam, 1 to 3 mg). Transthoracic echocardiography (TTE) to supplement gradient and valve area calculations was performed using the same system with 3MHz transducers. All echocardiographic examinations were performed at baseline and repeated after each thrombolytic treatment session.

Echocardiographic criteria. The echocardiographic criteria were as follows: prosthetic valve thrombus was recognized as soft and homogeneous, mobile or fixed echo densities located at the valve occluder and/or valve struts. The largest diameter of the thrombus as well as the length of the mobile portion, if present, were measured. A diagnosis of pannus formation was made when fixed, bright echodense structures, sometimes containing focal calcific deposits, were present primarily along the valve ring with extension into the valve orifice. Patients with valve dysfunction due to pannus formation were not included in this series (four patients in the same time period, all

confirmed at surgery).

Although different makes of mechanical valves will have different "normal gradient" ranges, we arbitrarily selected the cutoff points for valvular obstruction. These limits were largely based on the previously published values. The limitation of the occluder movement was evaluated subjectively. A significant narrowing of the prosthesis was diagnosed when the Doppler mitral valve area was <1.5 cm2 and the mitral valve mean gradient was >10 mm Hg, or when the aortic mean gradient was >40 mm Hg.

Patients with any thrombus, causing significant narrowing were accepted as candidates for thrombolysis. Thrombolytic treatment was contraindicated in patients with bleeding tendency and in those with expanding or hemorrhagic cerebral infarcts.

Tenecteplase was given at a fixed dose of 0.5mg/kg as a bolus over 10 minutes to all the patients. Heparin was started immediately in all the patients with ACT maintaining more than 250 in all the case. TTE was repeated at 6 hours and 24 hours to assess the response to therapy. Leaflets movement was assessed by fluoroscopy at 6 and 24 hours.

Definition of thrombolytic success. The response to thrombolytic treatment was defined as a complete when significant narrowing of the valve (based on hemodynamic measurements mentioned above) was no longer present and a >50% reduction in largest diameter of the thrombus mass was achieved.

Heparin and warfarin treatment was started and heparin therapy was continued until an international normalized ratio (INR) of >2.5 was achieved.

Statistical analysis :

Chi-square test and Student's *t* test were utilized for the comparison of discrete and continuous variables, respectively. A p value of <0.05 was accepted as significant.

RESULTS

The types of the prosthetic valves and clinical status at presentation were summarized in Table 1. Of the 12 symptomatic patients, 9 had mitral, 2 had aortic and 1 had both mitral and aortic valve prostheses. The etiology of valve disease was rheumatic in all patients except 1 who had bicuspid aortic valve with aortic stenosis. All patients had bileaflet prosthetic valve and were taking acenocumerol derivatives at presentation. The average interval between valve replacement and presentation was 144± 132 weeks (8 to 440weeks; median 93 weeks). INR at presentation were 1.79±0.34 and 2.53±1.31 for patients with aortic and mitral valve prosthesis. Three patients with mitral valve thrombosis had INR value >3.5 at presentation. Dyspnea (NYHA class III or IV) was the chief complaint in all the patients at presentation. No patients present with transient ischemic attack, stroke or syncopal attack.

Echocardiographic thrombolytic response

Hemodynamic measurement at baseline and follow up were summarised in table 2. At presentation, average mean gradient measured by colour Doppler was 43.3±13.01mmhg and 24.2±4.86mmhg for aortic and mitral valve prosthesis respectively. Following thrombolytic therapy, for aortic PVT mean gradient decrease to 14.1±4.2mmhg and 8±2.64 at 6hrs and 24hrs (p=0.001). For mitral PVT, mean gradient was 10.2±3.99mmhg at 6hrs and 5.88±2.57mmhg at 24hrs (p<0.001). All patients were clinically stable within 6hrs of thrombolytic therapy. On fluoroscopy, 7 (58.3%) patients had normal movements of both leaflets, whereas 5 (42.7%) had abnormal movement of one leaflet.

Complications of thrombolytic treatment

The complications of thrombolytic treatment were seen in 3(25%) patients. Major complications included CVA (1 infarct and 1 large infarct with small hemorrhagic transformation). There was no death or coronary embolisation. One patient had large sheath site hematoma and large hamatoma over right thigh which was managed conservatively. There was no minor bleeding in any patients.

Follow up

All patients were asymptomatic (NYHA class I) at 6 months follow up. Average mean gradient was 10.33±4.72mmhg for aortic valve prosthesis and 8.1±2.88mmhg for mitral prosthesis. All patients (including those having CVA) were stable on follow up.

DISCUSSION

PVT is defined as any obstruction of prosthesis by non infective thrombotic material. It has an estimated incidence of 0.03% - 4.3% per year[2] and is reported to occur in 0.5% - 8% of the left-sided prosthetic valves and in up to 20% of tricuspid prostheses [3,4]. The most common cause of PVT is inadequate anticoagulant therapy (in up to 82% of cases)[3]. Other pathogenic factors include: mitral position of the prosthesis; type of prosthesis; atrial fibrillation; left atrial enlargement; ventricular dysfunction; and multiple valve replacements [5]. Diagnosis of prosthetic heart valve thrombosis is made by a combination of clinical data (heart failure, absence of prosthetic sounds, cardiogenic shock), fluoroscopic examination (abnormal mobility of tilting disks) and echocardiographic (both transthoracic and transoesophageal) abnormalities (high prosthetic gradient, reduction of effective valve orifice area, lack of disk mobility and detection of thrombotic mass adherent to the prosthesis)[3,6]. Management of PVT remains controversial. There are currently no randomized controlled trials favoring surgery over thrombolysis and vice versa. Surgery, in the form of thrombectomy or valve replacement, remains the treatment of choice but carries a significant mortality ranging from 4.7% to 20% [2,3,7]. Thrombolysis, on the other hand, has emerged as an attractive alternative with reported success rates in the region of 75%-88% for PVT [2]. Our patient had stable hemodynamics which gave us a window of opportunity to use thrombolysis therapy. If this had been unsuccessful we would have proceeded with surgery. In addition, the patient had received his first MV replacement six months previously and we felt that, by giving him a trial of thrombolysis, we would have spared him the added burden of undergoing surgery twice in a short time period. The current treatment algorithms suggested by some authors include using thrombolysis for right sided PVT while using surgery for left-sided PVT[8,9]. They also recommend using thrombolytic therapy in left-sided PVT if surgery is contraindicated or if the patient is critically ill[9]. Others have reported that patients in the New York Heart Association functional classes I and II achieve the best results with thrombolytic therapy with the lowest incidence of peripheral embolism[10]. In our study, the use of tenecteplase proved useful in unstable patients with no increased risk. Following thrombolysis, all were placed on oral anticoagulant plus ecosprin (except those with CVA). We have started him on low-dose aspirin because coronary artery disease status was not assessed. Recent guidelines have suggested that in such cases the use of low-dose aspirin, in addition to oral anticoagulant, may decrease the chance of recurrence[11]. Thrombolytics reported in the literature are streptokinase, urokinase and recombinant t-PA (alteplase)[5]. There are no studies comparing these different thrombolytic agents in PVT[3,7]. The most important complications of thrombolytic therapy are thromboembolic events and cerebral hemorrhage. Thromboembolism is more frequent in left-sided prosthesis with an incidence of 9%-20%. Embolic complications occur in two forms: peripheral embolism and cerebral. Cerebral embolism has an overall incidence 3%-10% (more in the presence of atrial fibrillation). Cerebral hemorrhage rates fluctuate between 0%-3%[3,7]. Tenecteplase is a synthetically engineered variant of alteplase designed to have increased fibrin specificity, greater efficacy, increased resistance to plasminogen activator inhibitor-1 (PAI-1) and a longer half-life. It has been used extensively in acute myocardial infarction (including in our institute) but its use in PVT treatment has rarely been reported[1,3]. One advantage of tenecteplase is that its dosing is based on actual body weight which enhances both safety and efficacy outcomes by avoiding wider fluctuations in the drug plasma concentration. Compared to recombinant t-PA (for example, alteplase), tenecteplase use leads to lower rates of bleeding complications and a decreased risk of cerebral hemorrhage among high risk patients[12]. Tenecteplase, contrary to recombinant tissue plasminogen activators, has been synthetically modified which in turn has important clinical applications. The increased fibrin specificity theoretically enhances the enzymatic activity at the clot and reduces systemic fibrinolysis. Furthermore, the increased resistance to PAI-1, an enzyme secreted by platelets that inhibit thrombolytics, may enhance the efficacy of tenecteplase. This drug proved useful in our study where successful thrombolysis was achieved for mitral and aortic PVT with no increased risk to the patient.

Study Limitation

The main limitation of our study was small sample size of the patients. A large scale study will be required in the future to further support the use of this agent as first line management for PVT.

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