

Original Research Article

Study of prosthetic heart valve thrombosis and outcomes after thrombolysis

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ABSTRACT

Background: The study aimed to evaluate the clinical presentation, diagnostic features, treatment strategies, and complications of prosthetic heart valve thrombosis (PHVT) and to determine efficacy, outcomes and complications of thrombolytic therapy during hospital stay.

Methods: This was a prospective, observational, single-centre study carried out between March, 2016 and December, 2017 at a tertiary care centre in India. Total 110 patients with history of prosthetic heart valve replacement and symptoms related to PHVT were included in the study. Patients underwent thrombolysis, surgery or conservative management for treatment of PHVT, as per their individual clinical presentation. Clinical profile and treatment outcomes were assessed using a pre-tested, semi-structured questionnaire and clinical assessment.

Results: Mean age of the patients was 39.4±12.5 years. Most of the patients presented with NYHA class II and III (85.4%) symptoms. Total 20.9% of patients were poorly compliant with anticoagulants. Thrombolysis was initial treatment in 105 (95.5%) patients. Five (4.6%) patients were treated with heparin. Two patients underwent surgery after failed thrombolysis. Mortality in the thrombolysis group was 6.6%. Embolism occurred in 8.6% of the group and major bleeding in 1.9%. One patient who underwent surgery died.

Conclusions: In light of these results, it can be concluded that most cases of PHVT are due to inadequate anticoagulation and poor monitoring mainly in patients belonging to the lower socioeconomic group. Thrombolysis can be considered as first line therapy where the immediate surgical options are remote.

Keywords: Prosthetic heart valve, Streptokinase, Thrombosis, Thrombolysis

INTRODUCTION

Prosthetic heart valves have been a boon to the patients with valvular disorders. However, every boon comes with a bane, such that prosthetic valves have been associated with a perilous complication, prosthetic heart valve thrombosis (PHVT). The incidence of PHVT depends on myriad factors, contributing to 20% of tricuspid valve and 0.1% to 6% per patient-year of aortic and mitral valves.¹ In developing countries, incidence of PHVT

escalates even up to 10% per patient-year.² It contributes significantly to the late morbidity and mortality after heart valve surgery. Suboptimal anticoagulation, atrial fibrillation and severe LV dysfunction are the major causes for PHVT.³ The clinical presentation is variable and ranges from insidious dyspnea to cardiac arrest. It might be obstructive (allied with hemodynamic compromise) or non-obstructive (asymptomatic or accidental identification) thrombosis. The untreated mortality associated with this condition warrants rapid

diagnostic evaluation using the established as well as emerging techniques like transthoracic echocardiography, transesophageal echocardiography, cinefluoroscopy (for mechanical valves) and computed tomography.⁴

The appropriate management of PHVT has been still debatable. Some guidelines (European Society of Cardiology) recommend surgery for all, irrespective of clinical status, while some (Society of Heart Valve Diseases) recommend thrombolytic therapy for all patients without contraindications. Till date, there has been no class I recommendation in any guideline for management of PHVT due to no randomized controlled trials.⁵ In India, the exact rate of incidences of PHVT and its primary treatment preference has been lacking. The choice of the therapeutic modality for treatment of PHVT (heparin treatment, thrombolysis, surgery) has been largely influenced by the presence of valvular obstruction, by valve location (left- or right-sided), and by clinical status.⁶ Thus, this study aimed to evaluate the clinical presentation, diagnostic features, treatment strategies, and complications of PHVT and to determine efficacy, outcomes and complications of thrombolytic therapy during hospital stay.

METHODS

This was a prospective, observational, single-centre study carried out between March, 2016 and December, 2017 at a tertiary care centre in India. Total 110 patients were enrolled during this period. Patients with history of prosthetic heart valve replacement and symptoms related to prosthetic valve thrombosis admitted to ICU during the study period were included in the study. Patients with high gradient due to pannus (The visualization of an echogenic mass is almost universal in thrombosis, but only appears in 70% of obstructions caused by pannus. The echogenic characteristics of the mass are more important: it has an appearance of soft tissue (thrombotic material) in thrombosis, while it appears as hard tissue (fibrotic material) in the case of pannus. A thrombotic mass is usually larger than pannus. In mitral prosthetic thrombosis the mass frequently extends into the atrial endocardial surface, a feature rarely seen in obstruction caused by pannus); patients with infective endocarditis and vegetations; degenerated/ruptured prosthetic valve were excluded from the study. Informed consent was obtained from all patients included in the study. The study was approved by Institutional Ethics Committee.

Data collection

Data collection was started after obtaining clearance from the Institutional Ethics Committee. Preoperative clinical data, initial valve procedure, diagnostic features of valve thrombosis, and management before, during, and after the treatment, complications and follow-up were recorded. Clinical profile and treatment outcomes were assessed using a pre-tested, semi-structured questionnaire and clinical assessment.

All patients underwent routine blood investigations, electrocardiogram, and transthoracic echocardiography. Transesophageal echocardiography and fluoroscopy were done based on the clinical indication. The decision to either thrombolysis or undergo surgery was made after analysing the risks and merits in each case. It was based on a consensus agreement involving the cardiologist, cardiac surgeon and the patients' relatives.

Statistical analysis

Continuous variables were presented as mean \pm standard deviation and categorical variables as counts and percentages. All data were analysed using the Statistical Package for Social Sciences (SPSS; Chicago, IL, USA) program, version 15.

RESULTS

A total of 110 patients with prosthetic valve thrombosis were identified and analyzed in the study. Mean age of the patients was 39.4 \pm 12.5 years. Majorities were in the age group between 36 to 40 years and the least cases were in the age group of \leq 20 years. Majority of the patients were females (68; 61.8%) and 42 (38.2%) were males. The predisposing factor leading to valve replacement was rheumatic heart disease in majority (93.6%) of the patients. Most of the patients presented with NYHA class II and III (85.4%) symptoms (Table 1).

Table 1: Baseline demographics of patients.

Variables	N = 110 patients
Age, (Mean \pm SD, Years)	39.4 \pm 12.5
Male, n (%)	42 (38.2%)
Predisposing factor for native valve disease	
Rheumatic heart disease, n (%)	103 (93.6%)
Degenerative aortic valve, n (%)	7 (6.4%)
Comorbidities	
Pregnancy, n (%)	1 (0.9%)
Recent CVA, n (%)	6 (5.5%)
Anemia, n (%)	3 (2.7%)
Renal dysfunction, n (%)	2 (1.8%)
None, n (%)	98 (89.1%)
NYHA Class	
Class I, n (%)	1 (0.9%)
Class II, n (%)	46 (41.8%)
Class III, n (%)	48 (43.6%)
Class IV, n (%)	10 (9.1%)
Pulmonary edema, n (%)	3 (2.7%)
Asymptomatic, n (%)	2 (1.8%)
International Normalised Ratio (INR)	
<2, n (%)	61 (55.5%)
2-3, n (%)	25 (22.7%)
>3, n (%)	24 (21.8%)
Application of fluoroscopy, n (%)	28 (25.5%)
Application of transoesophageal echocardiography, n (%)	3 (2.7%)

Majority of the patients (55.5%) had an international normalised ratio (INR) in non-therapeutic range (<2). Acenocoumarol was the most commonly prescribed anticoagulant, followed by warfarin. Aspirin was added in 26.4% of patients. 20.9 % of patients were poorly compliant with drugs and monitoring of prothrombin time. More patients in economically underprivileged groups had discontinued medications when compared to those who were a better socioeconomic group. Almost all patients presented with symptoms. However, in 2 patients the diagnosis was made on routine follow up Echocardiogram. Twenty two patients (20.0%) had atrial fibrillation (AF) at presentation. Of these, in 5 patients the AF was documented to be new.

Table 2: Patients' characteristics related to valve.

Variables	N = 110 patients
Prosthetic valve position	
Mitral valve, n (%)	65 (59.1%)
Aortic valve, n (%)	25 (22.7%)
Double valve replacement-Mitral valve, n (%)	13 (11.8%)
Double valve replacement-Aortic valve, n (%)	7 (6.4%)
Prosthetic valve type	
St. Jude, n (%)	52 (47.3%)
Medtronic ATS, n (%)	27 (24.5%)
TTK Chitra, n (%)	21 (19.15%)
Bioprosthetic, n (%)	1 (0.9%)
Others, n (%)	9 (8.2%)
Recurrent valve thrombosis	
Twice, n (%)	3 (2.7%)
Once, n (%)	16 (14.5%)
Never, n (%)	91 (82.7%)
Time of presentation after valve replacement	
<6 months, n (%)	11 (10.0%)
6 months - 1 year, n (%)	16 (14.5%)
1-2 years, n (%)	21 (19.0%)
2-3 years, n (%)	13 (12.0%)
3-4 years, n (%)	7 (6.4%)
4-5 years, n (%)	9 (8.1%)
> 5 years, n (%)	33 (30.0%)
Anticoagulant	
Acenocoumarol	76 (69.1%)
Acenocoumarol + Aspirin	29 (26.4%)
Warfarin	5 (4.5%)
Drug compliance	
Good	87 (79.1%)
Poor	23 (20.9%)

Mitral prosthesis was most commonly involved (59.1%) followed by aortic valve (22.7%) (Table 2). Most of the study participants (91; 82.7%) presented with first time thrombosis after surgery. Sixteen (14.5%) patients had a prior history of prosthetic valve thrombosis and 3 (2.7%) of them had 2 prior episodes. Majority of patients (33;

30%) presented after five years of surgery.

Treatment

In all cases the decision to thrombolyse, operate or continue conservative management was taken by a combined decision by the team of senior cardiologists and cardiac surgeons taking into consideration the hemodynamic stability and functional class of each patient. The treatment options were also discussed with the patients and their relatives. Thrombolysis was the initial treatment in 105 (95.5%) patients. Five (4.6%) patients were treated with only heparin. Two patients underwent surgery after failed thrombolysis. Streptokinase was the most commonly used agent to thrombolyse 82 (78%) patients. The remaining 23 (22%) were treated with urokinase. Both streptokinase and urokinase were given as bolus followed by infusion. The duration of infusion was based on the clinical response and complications. The regimen in our study was a 250000 unit bolus, followed by 100000 units per hour infusion till clinical response. Infusion was stopped if there was no response to treatment after a variable period of 24 to 36hours. Duration of lysis was 12-24hours in most of the patients (61; 55.5%) (Table 3).

Table 3: Details of treatment given to the patients.

Variables	N = 110 patients
Treatment	
Thrombolysis, n (%)	105 (95.5%)
Heparin (Conservative), n (%)	5 (4.6%)
Thrombolysis and surgery, n (%)	2 (1.8%)
Thrombolytic used	
Streptokinase, n (%)	82 (78.0%)
Urokinase, n (%)	23 (22.0%)
Dose of thrombolytic agent	
Bolus dose (x 10 ⁵ units) over one hour	2.5
Infusion dose/hour (x 10 ⁵ units)	1.0
Duration of lysis	
< 12 hrs, n (%)	10 (9.1%)
12-24 hrs, n (%)	61 (55.5%)
24-48 hrs, n (%)	39 (35.5%)

Of the 105 patients who underwent thrombolysis, complete response was achieved in 90.5% of the patients. Mortality in the thrombolysis group was 6.6%. Embolism occurred in 8.6% of the group and major bleeding in 1.9% (Table 4). Two patients had to undergo redo valve surgery after failure to establish normal prosthetic valve movement. Two patients (1.8%) underwent surgery for failed thrombolysis in this study. Among the surgical group one patient improved and one patient died due to major intracranial bleed. The most common complication in the study group was embolism followed by bleeding manifestations. Most of the embolic manifestation resulted in a cerebro-vascular accident (CVA) (Table 5). Overall the mortality in the entire group was 8.1%. Seven patients died in thrombolysis group. One patient died in

the surgical group. Two of the five patients who underwent conservative management died.

Table 4: Outcomes after thrombolysis in 105 patients.

Outcomes	Urokinase (n = 23)	Streptokinase (n = 82)	Total (N=105)
Success, n (%)	21 (91.2%)	74 (90.2%)	95 (90.5%)
Embolism, n (%)	01 (4.4%)	8 (9.7%)	9 (8.6%)
Bleed, n (%)	0	2 (2.4%)	2 (1.9%)
Mortality, n (%)	01 (4.4%)	6* (7.3%)	7 (6.6%)

(*patients who died due to bleed or embolism or later were also included)

Table 5: Overall complications and mortality (N = 110).

Complications	N = 110
None, n (%)	86 (78.3%)
Cerebro-vascular accident (Bleed), n (%)	3 (2.7%)
Cerebro-vascular accident (Infarct), n (%)	12 (10.9%)
Peripheral embolism, n (%)	3 (2.7%)
Sepsis, n (%)	3 (2.7%)
Mortality, n (%)	
Thrombolysis (105)*, n (%)	7 (6.6%)
Surgery (2)*, n (%)	1 (50%)
Conservative (5), n (%)	2 (40%)
Others, n (%)	3 (2.7%)

(*2 patients underwent thrombolysis and surgery)

DISCUSSION

Thrombosis is a serious complication of prosthetic heart valve replacement and incurs high mortality. Early diagnosis and appropriate management are paramount in reducing mortality due to such complication. In this study, the single-center experience of 110 cases of PHVT treated over a period of 19 months has been reported. In this study PHVT was more common in women (61.8%). Parallely, many studies from India have shown that women have been more predisposed to PHVT.⁷

In this study mitral prosthesis was most commonly involved (59.1%) followed by aortic (22.7%). In the study by Gupta et al, 87.3% of the PHVT episodes occurred in the mitral position.⁸ Similarly several studies have confirmed that incidences of mitral prosthetic valve thrombosis have been 2-3 times higher than thrombosis of an aortic prosthesis.^{6,9} In this study overall 20.9% of patients were poorly compliant with anticoagulants and monitoring of prothrombin time. Most of them stopped medications and monitoring due to financial constraints and negligence. In a recent study by Karthikeyan G et al, 72% (79/110) of the patients had inadequate anticoagulation at presentation.² This highlights the

problems of valve replacement in a developing country such as India where majority of the population is economically underprivileged.

Streptokinase was the most commonly used (78%) agent for thrombolysis. The remaining 23 (22%) patients were treated with urokinase. Successful thrombolysis as satisfying the strict criteria of “decrease in prosthetic valve gradient to baseline with normal prosthetic movement and in the absence of complications, need for surgery or death” was achieved in 90.5% of the patients. Mortality in the thrombolysis group was 5.7%. Similarly, consensus statements on the treatment of PHVT and recent systematic reviews, suggest that the success rate with fibrinolytic therapy is at least 80%(10-12). Moreover, Sharma and Mewada in a study on 48 patients used streptokinase and reported 81% success and 8% mortality.¹³ Singh S et al, also used streptokinase in 44 patients with PHVT and reported 73% success and 6.8% mortality.¹⁴

Embolism occurred in 8.6% of patients who were thrombolysed. Other studies have shown an embolic risk of 12% to 17% caused by thrombolysis.^{15,16} Two patients underwent surgery in this study. Both of these patients underwent thrombectomy and redo valve replacement. One patient improved and other patient died due to major bleeding. Studies have shown that the mortality rate of surgery vary with functional class. It has been 4% in patients with NYHA class I and upsurges as high as 69% in patients with NYHA class IV symptoms.¹² In this study, 2 of the 5 patients who underwent conservative strategy died (mortality rate 40%). This reinforces the dictum that conservative strategy must be used only in asymptomatic patients with non-obstructive PHVT with an overall minor clot burden.

In summary, the patients in this study who presented with class II and III symptoms responded well towards thrombolysis. Patients who presented in advanced state with acute pulmonary edema had unfavourable outcome after thrombolysis.

CONCLUSION

In light of these results, it can be concluded that most cases of PHVT are due to inadequate anticoagulation and poor monitoring mainly in patients belonging to the lower socioeconomic group. Thrombolysis can be considered as first line therapy where the immediate surgical options are remote. Treatment with thrombolysis has successful hemodynamic and clinical response in majority of patients. Videos of stuck valves can be shown and explained to the patients about the consequences of stuck valve, including death. It should also be explained that second surgery will be associated with higher morbidity and mortality due to adhesions. A dedicated prosthetic valve clinic can be run where the importance of continuing anticoagulants can be emphasised during every follow up visit.

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