Clinical Profile of Patients with Prosthetic Heart Valve Thrombosis Undergoing Fibrinolytic Therapy and NYHA Class as a Predictor of Outcome

Sanjeev Bhatia [1], Sharad Jain [1], Vishal Sharma [1], Zeeshan Mansuri [1,*], Krutika Patel [2], Pragya Jain [3], Mithilesh Kulkarni [1], Tanmay Agrawal [1], Kamal Sharma [1]

[1] Department of Cardiology, U. N. Mehta Institute of Cardiology and Research Centre (UNMICRC), Civil Hospital Campus, Asarwa, Ahmedabad-380016, Gujarat, India
[2] Department of Research, U. N. Mehta Institute of Cardiology and Research Centre (UNMICRC), Civil Hospital Campus, Asarwa, Ahmedabad-380016, Gujarat, India
[3] NHL Medical College, VS General Hospital, Paldi, Ahmedabad, Gujarat 380006, Gujarat, India

** Corresponding author: Zeeshan Mansuri, Department of Cardiology, U. N. Mehta Institute of Cardiology and Research Centre (UNMICRC), Civil Hospital Campus, Asarwa, Ahmedabad-380016, Gujarat, India. E-mail: zzeeshan2001@gmail.com*

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Abstract

Introduction: Prosthetic heart valve thrombosis (PHVT) is a major complication in patients with mechanical prosthetic heart valve which occurs primarily due to ineffective anticoagulation. This study aimed to evaluate the clinical profile of the patients presenting with PHVT undergoing fibrinolytic therapy and analyzing patients with respect to New York Heart Association (NYHA) functional class on presentation and its association with outcome of fibrinolytic therapy.

Methods: This was prospective, observational study conducted from June, 2016 to April, 2018. Total 133 patients with prosthetic heart valve thrombosis were included. Routine blood investigations included complete hemogram, liver and renal function tests. Prothrombin time with INR was done on admission. The diagnosis of PHVT was assessed by cine-fluoroscopy (CF) and/or echocardiography (transthoracic/transesophageal). Follow-up at 6 months was scheduled for all patients.

Results: All patients received fibrinolytic therapy in which 108 (81.2%) were treated with streptokinase and 25 (18.8%) were treated with urokinase. On presentation, 48.9% patients were in NYHA class III, 41.4% in NYHA class IV and 9.77% in NYHA class II. Fibrinolytic therapy was successful in 105 patients (78.9%) and it failed in 28 patients (21.1%). Mortality in NYHA class II was 0%, NYHA class III was 4.6% and in NYHA class IV was 23.6%. During 6 months follow up prosthetic heart valve thrombosis recurred in 12 (11.43%) patients.

Conclusion: From our single center experience, fibrinolytic therapy is effective first line therapy for prosthetic heart valve thrombosis and NYHA functional class on presentation can predict the outcome of fibrinolytic therapy.

INTRODUCTION

Prosthetic heart valve thrombosis (PHVT) is a rare but often deadly complication of valve replacement related to morbidity and mortality after valve replacement. Globally, the prosthetic heart valve implantation rate is increasing 5-7% per year [1]. There is about 10% prevalence of left-sided PHVT, upon screening of

around 1000 post-operated patients [2]. The clinical presentation is variable and ranges from insidious dyspnea to cardiac arrest. It might be obstructive or non-obstructive thrombosis [3]. Obstructive thrombosis is related with hemodynamic compromise and non-obstructive thrombosis is usually asymptomatic or accidental identification. The obstruction of a mechanical prosthesis mostly necessitates aggressive treatment with surgery or fibrinolysis, as the administration of anticoagulants will generally be insufficient. Due to the absence of larger prospective studies, the choice of treatment for PHVT remains controversial.

As per the American College of Cardiology/ American Heart Association guidelines, surgery should be the preferred treatment strategy for left-sided PHVT. Fibrinolytic therapy should be administered only to patients with poor functional class (NYHA class III or IV), and those with high surgical risk or contraindications to surgery. If the prior heparin treatment fails to manage the patients, fibrinolytic therapy can also be considered in such patients with good functional class (NYHA class-I or II) and a small thrombus load. Several studies have been done for prediction of the success rates and improving the risk stratification for patients undergoing fibrinolysis [2, 4, 5].

In some studies, NYHA functional class, level of obstruction, valve location (left- or right-sided) and thrombus size were recognized as the predictors of fibrinolytic success [6, 7]. We studied the clinical profile of the patients presenting with PHVT undergoing fibrinolytic therapy. As, the NYHA functional classification is used to describe the severity of clinical status in patients with heart failure with dyspnea and/or angina, the main aim of this study is to evaluate the patients of PHVT with respect to NYHA functional class on presentation and its association with outcome of fibrinolytic therapy.

MATERIALS AND METHODS

This was a prospective, observational study conducted in the department of cardiology at our institute, from June, 2016 to April, 2018. Total 133 patients with PHVT were enrolled. The study was approved by institutional ethics committee. We prospectively enrolled the data of patients admitted with valve replacement and having history suggestive of prosthetic valve dysfunction in form of recent onset acute or subacute dyspnea (< 1 month) or embolic phenomena were subjected to evaluate for prosthetic heart valve thrombosis. Patients with confirmed diagnosis of valve thrombosis either by transthoracic/transesophageal echocardiography or cine-fluoroscopy were included in our study. Patients with gradual or chronic history suggestive of valve dysfunction were excluded. Patients with prosthetic valve endocarditis were also excluded. A written informed consent was taken from all the subjects.

Routine blood investigations included complete hemogram, liver and renal function tests. Prothrombin time with INR was done on admission and previous record of anticoagulation was noted if available. On admission, detailed transthoracic echo evaluation was performed. For mitral prostheses, a mean gradient > 10 mm Hg and an effective area (< 1 cm^2) was indicative of PHVT. For aortic prostheses, criterion for PHVT was a mean gradient > 45 mm Hg. Serial echocardiography was performed after fibrinolytic therapy to evaluate resolution of thrombus and transprosthetic valve gradient.

In fibrinolytic therapy all details of fibrinolytic therapy were noted (e.g. fibrinolytic agent, dose, duration, complications, etc.). Streptokinase (SK) and Urokinase (UK) have been the most used fibrinolytic agents. Patients with known allergy to SK or those who have been exposed previously to SK were given UK.

Fibrinolytic Regimen

Streptokinase: 250,000-U bolus given in 30 min, followed by an infusion of 100,000 U/h.

Urokinase: 4,400 U/kg bolus over 30 min followed by 4400 U/kg per hour

Statistical Analysis

All statistical studies were carried out using IBM SPSS program vs 20. Quantitative variables were expressed as the mean ± standard deviation and qualitative variables were expressed as percentage (%). Parametric values between two groups were performed using the independent sample t-test or chi-square test, as appropriate. Univariate and multivariate logistic regression was used to find out factors associated with outcome. Categorical variables were compared using the chi-square test. A nominal significance was taken as a two tailed p value < 0.05.

RESULTS

The study population consisted of 45 (33.8%) males and 88 (66.2%) females, with mean age of 38.4 ± 12.4 years. Range of average hospital stay of 117 discharged patients was 4-29 days with mean 11.05 days. The mean interval between the first implantation and valve thrombosis was 25.2 months (range 64 days to 11 years). The baseline characteristics of the study are mentioned in Table 1.

Every patient was tested on admission for prothrombin time and INR. Out of 133 patients 90 patients (67.7%) were inadequately anticoagulated on admission while 43 (32.3%) patients admitted with adequate anticoagulation. Each patient underwent detailed transthoracic echocardiography evaluation and was evaluated serially for treatment monitoring. Majority of patients (69.2%) had dilated left atrium on admission. 73.8% of patients had good LV function, only 12.4% patients had moderate to severe LV dysfunction.

Around 44.6% patients had moderate to severe PAH on admission. Transthoracic 2D echocardiography was done in all 133 patients, additionally cine-fluoroscopy and transesophageal echocardiography were used in 93 (71.5%) and 9 (6.9%) patients, respectively. In 23 (17.8%) patients, both cine-fluoroscopy and transesophageal echocardiography were used in addition to trans thoracic echocardiography. The TEE was more helpful to rule out pannus formation or non-thrombotic causes for prosthetic valve dysfunction.

Atrial fibrillation or flutter was present in 36.9% patients and remaining 63.1% had sinus rhythm. On presentation, 48.9% patients were in NYHA class III, 41.4% in NYHA class IV and 9.8% in NYHA class II. Mortality in NYHA class II was 0%, NYHA class III 4.6% and in NYHA class IV 23.6%.

Thrombosis in valves included 103 (77.4%) bi-leaflet valves, 29 (21.8%) tilting disc valves and 1 (0.8%) ball cage valve. 98 (73.7%) patients had history of MVR, 13 (9.7%) had history of AVR, 20 (15.0%) had history of DVR (mitral and aortic) and 2 (1.5%) patients had TVR (mitral, aortic, and tricuspid). Of 20 patients with DVR, 15 had mitral valve thrombosis and 5 had aortic valve thrombosis. Of TVR patients, both had tricuspid valve thrombosis.

All patients received fibrinolytic therapy of which 108 (81.2%) were treated with streptokinase and 25 (18.8%) were treated with urokinase. Duration of fibrinolytic therapy ranged from 1-48 hours. Average duration of fibrinolytic therapy was 33.09 hours. Fibrinolytic therapy was successful in 105 patients (78.9%) and it failed in 28 patients (21.1%). In hospital mortality was 12.03 % (16 patients), 12 patients went for redo surgery after failure of fibrinolytic therapy.

Mortality was significantly higher in NYHA class IV (23.6%) patients compared to class II or III patients (P = 0.007 and 0.04, respectively). Thus, NYHA functional class was found to be strong independent predictor of outcome of patient irrespective of treatment modality. Successful fibrinolytic therapy was achieved in 100% patients with NYHA class II, 89.2% in NYHA class III and 61.8% in NYHA class IV. After treatment only 8.7% patients had residual moderate PAH. Total 117 patients were followed up to 6 months after discharge. Out of 117, 12 (11.4%) patients developed recurrence of PHVT.

In univariate analysis, factors associated with mortality were complications and NYHA functional class (P = 0.002) (Table 2). In NYHA class III group, 3 patients developed complications, of which one patient developed hypersensitivity reaction to streptokinase and 2 patients developed hemorrhagic complications. One patient developed intra cerebral hemorrhage and 1 developed gum bleeding. In NYHA class IV group, total 13 patients developed complications. Six patients developed cardio-embolic complications of which 4 patients developed TIA/stroke, and 2 patients developed peripheral embolization. Hemorrhagic events were seen in 7 patients with NYHA class IV group, of which 5 patients developed intra cerebral hemorrhage, 1 patient developed hematuria and 1 patient developed epistaxis. No association was observed with age, sex, palpitation, and valve type. In multivariate analysis, by logistic regression the only factor associated with mortality was NYHA functional class (95% CI -0.23 to -0.07, P = 0.0001).

Table 1. Baseline Characteristics

Parameters	N=133(%)
Age, years	38.4 ± 12.4
Sex	
Male	45 (33.8)
Female	88 (66.2)
Type of Prosthetic valve	
Bileaflet	103 (77.4)
Tilting disc	29 (21.8)
Ball cage	1 (0.8)
NYHA class	
Class-II	13 (9.77)
Class-III	65 (48.87)
Class-IV	55 (41.35)
Cardiac rhythm	
Sinus	84 (63.16)
Atrial fibrillation	49 (36.84)
Inadequate anticoagulation	90 (67.67)
Fibrinolytic agent	
Streptokinase	108 (81.2)
Urokinase	25 (18.8)

Data in table are presented as Mean ± SD or No. (%)

Table 2. Distribution According to NYHA Class

Variables	NYHA Class-II n = 13 (%)	NYHA Class-III n = 65 (%)	NYHA Class-IV n = 55 (%)	P Value
Age, years	35.1 ± 16.7	37.5 ± 12.8	39.9 ± 12.6	0.39
Male	3 (23.1)	22 (33.8)	20 (36.4)	0.75
Female	10 (76.9)	43 (66.2)	35 (63.6)	0.66
Complication	0	3 (4.6)	13 (23.6)	0.002*
Failed fibrinolysis	0	7 (10.8)	21 (38.2)	0.0002*
Discharge	13 (100)	62 (95.4)	42 (76.4)	0.002*

*P-value < 0.05 shows statistical significance

Data in table are presented as Mean ± SD or No. (%)

DISCUSSION

Majority of patients in our study were relatively young. Around 60% patients were below 40 years of age. Reason for this is high prevalence of rheumatic heart disease (RHD) in young patients in our country and that's why majority of patients undergoing valve replacement are relatively young compared to developed countries. Many studies from India have shown that females are more predisposed to PHVT [8].

The most common risk factors leading to development of PHVT are inadequate anticoagulation, atrial fibrillation, left ventricular dysfunction, early post-operative period and pannus or vegetation [9]. The occurrence of PHVT is higher in left sided valves, mitral valve than aortic valve. Present study showed mitral prosthesis was most involved (73.7%) followed by AVR (9.8%). In a study by Gupta et al, 87.3% of the PHVT episodes occurred in the mitral position. Several studies have confirmed that mitral PHVT is twice or thrice more frequent than an aortic PHVT [8, 10].

In this study, overall, 90 (67.7%) patients showed inadequate anticoagulation. Similar observations were also found in studies conducted in developing countries such as Cuba and Nepal where the rates of inadequate anticoagulation were high (75% and 69.6%, respectively) [11, 12]. Other studies from India showed variable rates of inadequate anticoagulation ranging from 41.5% to 90.3% [13]. Streptokinase was the most used (81.2%) agent for fibrinolysis. The remaining 25 (18.8%) patients were treated with urokinase. Recent studies on using fibrinolytic therapy in treating PHVT showed favorable results proposing it to be applied as the first line of management, however data from any randomized controlled trials are deficient [6, 10]. Study done by Kathivel et al. used streptokinase compared to tenactaplace for left-sided PHVT. Complete success rate of fibrinolytic therapy was almost equal in both groups (77.5%). The study reported that Tenecteplase can be used for fibrinolytic therapy of PHVT in place of streptokinase with equivalent efficacy and at the alike rate of occurrence of any complication [14]. Present study showed similar success rate for streptokinase (78.5%).

Literature states that fibrinolysis has been an appropriate alternative to surgery for treatment of PHVT in India, which was also found in our study. Accordingly, in the recent PHVT guidelines of the Society of Heart Valve Disease, fibrinolysis was recommended as first-line therapy in all PHVT patients having thrombus diameter ≥ 5 mm, irrespective of the obstruction and NYHA functional class, and surgery must be reserved only for patients with failed fibrinolysis or in patients who indicate contraindication to fibrinolysis [2]. Another guideline, American College of Chest Physicians suggests fibrinolysis to be considered as the first choice for PHVT with thrombus burden <0.8 sq.cm; regardless of NYHA class [15]. Recently, the updated American College of Cardiology/American Heart Association guidelines report that choice of fibrinolysis or surgery should be dependent on multiple factors such as NYHA class, thrombus burden, contraindications to fibrinolysis, surgical risk, and recurrence [4].

Fibrinolysis possess various benefits like simplicity, easy availability, and comparative low cost. The success rate upon application of fibrinolysis has been variable as reported by previous Indian studies. It ranged from 59% to 100%, with an average rate of 78.1% success. However, the mortality rate was found to be between 1.9% and 9.5%. The incidences of major complications due to fibrinolysis included thromboembolism, major bleed, and anaphylaxis (8.4% to 18.7%) while minor complications included minor bleed, fever, etc. (2.3% to 25%) [10, 14, 16-18]. Present study supports the previous study reports; complete success in fibrinolytic therapy was observed in 101 patients (75.9%), with 13.2% complications and in-hospital mortality.

Present study showed total 133 patients with fibrinolytic therapy, complete clinical success achieved in 100% patients with NYHA class II, 89.2% in NYHA class III and 61.8% in NYHA class IV. We observed 12.0% mortality and 11.4% recurrence during follow up. From 12 patients (11.4%) who developed recurrence of PHVT, seven underwent surgery, five were given urokinase; one patient expired in surgical group and three patients expired in urokinase group. Most of the patients who died presented with NYHA class-IV (N = 13). As compared to other studies, the relatively high mortality rate due to majority (92.3%) of patients presenting in NYHA class III/IV. Study done by Nawale et al. also had small sample size but the patients presenting with NYHA class III and IV in that study were 38.1% and 52.4%, respectively [13]. In 2009, study of 68 patients' fibrinolytic success was achieved in 85% of patients, with an equally high success rate of 80% among NYHA class IV and class III patients; which correlates to present study. Recurrence rate was high (22%) than present study [19]. Similarly, One Indian study conducted by Patil et al. achieved 90.5% successful fibrinolytic therapy with 5.7% mortality [8]. Complications of fibrinolytic therapy, redo surgery, and failed fibrinolysis were frequently seen in NYHA class IV. In hospital mortality was also significantly higher in patients with NYHA class IV. These findings confirm that NYHA functional class is an important predictor of outcomes.

CONCLUSION

Considering results from our single center experience, fibrinolytic therapy can be considered as an effective first line therapy for prosthetic heart valve thrombosis. Moreover, the NYHA functional class on presentation can predict the outcome of fibrinolytic therapy.

Conflict of Interests

There is no competing interest

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