THROMBOLYTIC THERAPY IN PROSTHETIC VALVE THROMBOSIS; EFFICACY AND OUTCOME

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ABSTRACT

Objective: To determine the efficacy of thrombolytic therapy and its complications in PVT.
Study Design: Prospective cross-sectional study.
Place and Duration of Study: Study was conducted at AFIC/NIHD Rawalpindi from first Jan 2016 to Dec 2017.
Material and Methods: A total of 51 patients admitted with Prosthetic valve thrombosis PVT were enrolled in this study, through non-consecutive sampling technique. The primary outcome was complete response to thrombolytic therapy. The secondary outcome was a composite of death, Central nervous system CNS embolism, non CNS systemic embolism or major bleeding.
Results: Mean age was 40.88 (± 11.72). Twenty (43.13%) were male while 29 (56.86%) were female. Mitral PV was involved in 40 (78.4%) and aortic in 11 (21.6%). About 21 (41.2%) were in NYHA-I class and 29 (58.8%) in NYHA-III/IV class. All had bileaflet valve with involvement of one leaflet in 36 (70.6%) and both leaflet in 15 (29.4%). International normalized ratio INR was sub therapeutic in 37 (72.5%). Complete response was observed in 24 (47.05%) while secondary outcome was seen in 15 (29.41%) with death in 13 (25.49%) and CNS embolism in 2 (3.92%). There was no case of non-CNS embolism or major bleeding. Complete responses varied with the severity of patient and was 14 (66.66%) in NYHA–I/II and 10 (28.57%) in NYHA-III/IV, with *p*-value 0.044.
Conclusion: This study reveals the burden of prosthetic valve thrombosis in a developing country. It also reveals a high mortality and a suboptimal response to thrombolytic therapy. This study also underscores the advanced stage in which patients present.

Keywords: Fibrinolysis, Prosthesis, Thrombosis, Valves.

INTRODUCTION

Prosthetic valve PV implantation is at risk of prosthetic valve thrombosis PVT, a serious complication with a high morbidity and mortality. Its incidence varies from 0.3 to 1.3 per 100 patient years in developed countries[1] to 6.1% in developing countries[2]. Mechanical prosthetic heart valve MHV obstruction may be caused by thrombus formation, pannus in-growth, or a combination of both[3]. Urgent diagnosis, evaluation, and therapy are indicated because rapid deterioration can occur if there is thrombus causing malfunction of leaflet opening. Initial evaluation includes Transthoracic echocardiography TTE followed by Transesophageal echocardiography TEE in cases with suboptimal findings. TEE has a greater diagnostic accuracy over TTE[4]. Fluoroscopy provides accurate assessment of opening angle and mobility of MHVs. Bioprosthetic heart valves BHVs being radiolucent are not assessed with fluoroscopy[4]. Multidetector computed tomography is of value when TTE and TEE are inconclusive. It not only provides an accurate evaluation of the prosthetic valve structure and functional status, but is also helpful in identifying masses amenable to thrombolysis[5].

Current guide lines recommend fibrinolytic therapy if the thrombus is less than 14 days old, the patient has NYHA class I-II symptoms and thrombus is small I size (<0.8 cm2)[6,7].

The purpose of this study was to evaluate efficacy of thrombolytic therapy with

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streptokinase in PVT. In addition it will determine the frequency of complications in these patients.

MATERIAL AND METHODS

This is a prospective cross-sectional study carried out at AFIC/NIHD Rawalpindi from January 2016 to December 2017. Institutional ethical review board approval was obtained. Verbal consent was obtained from patients. Data collection tool was developed to measure demographics, response to treatment and outcome. PVT was suspected clinically in patients with dyspnea or chest pain or both with duration less then 14 days. Definitive diagnosis was based on fluoroscopy revealing immobile or hypomobile leaflets with or without increased pressure gradient on Doppler echocardiography[9]. Transesophageal echocardiography was carried out where it was feasible. Patients with contraindication to fibrinolytic therapy i.e. any previous intracranial hemorrhage, ischemic stroke within the last 3 months, presence of a left atrial thrombus on transthoracic echocardiography, and pregnancy were excluded.

Patients were advised IV heparin followed by IV streptokinase 0.25 MU over 30 minutes followed by 0.1 MU/hr infusion. Serial TTE was carried out and SK infusion was stopped on symptomatic improvement and improvement in leaflet movement and significant improvement in trans-valvular gradient. Infusions of streptokinase were continued for up to 72 hours depending upon the response and development of complication.

Outcomes

The primary outcome was the occurrence of a complete response to thrombolytic therapy. Secondary outcome was a composite of death, major bleeding, Central nervous system CNS embolism, or non–CNS systemic embolism. Patients were monitored for adverse events until they were discharged from the hospital.

Operational Definition

Complete response was defined as complete normalization of valve function in the absence of death, major bleeding, or embolic stroke. Complete normalization of valve function was defined as normal leaflet motion on fluoroscopy and normalization of trans-valvular pressure gradients on Doppler echocardiography. Partial response was defined as >50% improvement in trans-valvular gradients from baseline but with incomplete normalization of leaflet motion on fluoroscopy. Fibrinolytic therapy failure was defined as reduction in transvalvular gradient by less than 50%, persistent leaflet motion abnormality on fluoroscopy or if death occurred. Early valve thrombosis was defined as valve thrombosis occurring within 12 months of surgery.

Statistical analysis was carried out on IBM SPSS version 23. Categorical data was presented as percentages and frequency whereas descriptive statistics were expressed as mean and standard deviation for quantitative analyses. Chi square test was applied to analyze the data. A *p*-value of ≤0.05 was considered statistically significant.

RESULTS

From January 2016 to December 2017, 51 patients with PVT were enrolled. All had diagnosis confirmed on fluoroscopy and underwent Echocardiography. Baseline characteristics are shown in table-I: Mean age was 40.88 (± 11.72). 22 (43.13%) were male while 29 (56.86%) were female. Mitral PV was involved in 40 (78.4%) and aortic in 11 (21.6%). 21 (41.2%) were in NYHA-I/II class and 29 (58.8%) in NYHA-III/IV class. All had bileaflet valve with involvement of one leaflet in 36 (70.6%) and both leaflet in 15 (29.4%). International normalized ratio INR was subtherapeutic in 37 (72.5%). Metallic valve was involved in 98%. Late valve thrombosis was observed in 84.3%.

Efficacy of Streptokinase

Complete response was observed in 24 (47.05%) while secondary outcome was seen in

15(29.41%) with death in 13 (25.49%) and CNS embolism in 2 (3.92%). There was no case of non-CNS embolism or major bleeding. Complete responses varied with the severity of patient and was seen in 14 (66.66%) of NYHA –I/II and in 10 (28.57%) of NYHA-III/IV, with *p*-value 0.044 as shown in table-II .

Table-I: Baseline Caharaceristics.

Characteristic	No (%)
Age mean	40.88 (± 11.72)
Gender	
Male	22 (43.13%)
Female	29 (56.86%)
Valve involved	
Mitral	40 (78.4%)
Aortic	11 (21..6%)
Valve type	
Metallic	50 (98%)
Bioprosthetic	1 (2%)
Post surgery	
Early	8 (15.7%)
Late	43 (84.3%)
Severity	
NYHA I/ II	21 (41.2%)
NYHA III/IV	29 (58.8%)
Number of leaflet involved	
Single	36 (70.6%)
Double	15 (29.4%)
INR	
Therapeutic	14 (27.5%)
Subtherapeutic	37 (72.5%)
Response	
Complete	24 (47.05%)
Partial	13 (25.49%)
Failed	14 (27.45%)
Secondary outcome	15 (29.41%)
Death	13 (25.49%)
CNS/non-CNS embolism	2 (3.92%)

DISCUSSION

Prosthetic valve thrombosis PVT is a serious complication of PV, and has a high mortality. Early diagnosis is paramount in guiding management. Our study represents single center study in a developing country enrolling 51 patients with PVT over two years. The study evaluated efficacy of standard infusion of streptokinase in prosthetic valve thrombosis. Our main findings include an overall complete response in 24 (47.05%) while secondary outcome was seen in 15 (29.41%) with death in 13 (25.49%) and CNS embolism in 2 (3.92%). There was no case of non-CNS embolism or major bleeding. Complete responses varied with the severity of patient and was seen in 14 (66.66%) of NYHA-I/II and in 10 (28.57%) of NYHA-III/IV, with *p*-value 0.044 . Complete response of 47.05% in our study is below generally reported in studies. Consensus

statements suggest at least 80% success rate with fibrinolytic therapy[8]. Complete hemodynamic success was achieved in 76.3% of the 93 obstructed valves in an international multi-center registry (PRO-TEE study), in which thrombolytic agents used were streptokinase (54.7%), urokinase (17%), and t-PA (28.9%). Thrombolytic success was similar among different valves and lytic agents[4]. Relatively low complete response observed in our study is due to a high number of cases in advanced NYHA class III/IV and in circulatory shock at presentation. In our study only streptokinase was used.

Alternative streptokinase administration technique and alternative fibrinolytic agents: In a randomized controlled trial by Karthikeyan et al compared an accelerated infusion with the conventional infusion of streptokinase in 120 patients. Complete clinical response occurred in 38 (64.4%) of 59 patients with the accelerated infusion compared with 32 (53.3%) of 60 with the conventional infusion (hazard ratio 1.6, 95% confidence interval 0.9 to 2.5, *p* 0.055). There was no significant difference in the occurrence of the composite secondary outcome (hazard ratio 1.4, 95% confidence interval 0.5 to 3.5, *p* 0.50) or major bleeding (hazard ratio 2.2, 95% confidence interval 0.6 to 7.7, *p* 0.24) with the accelerated infusion. The success rate with fibrinolytic therapy was low overall (59%) and very low in patients in New York Heart Association functional class III/IV (24%)[9]. In another study by Ozkan et al streptokinase was compared with tissue plasminogen activator t-PA , with 182 consecutive patients divided into 5 groups. These included rapid (group-I), slow (group-II) streptokinase, high-dose (100 mg) tissue plasminogen activator (t-PA) (group-III), a half-dose (50 mg) and slow infusion (6 h) of t-PA without bolus (group-IV), and a low dose (25 mg) and slow infusion (6 h) of t-PA without bolus (group-V). According to this study, low dose (25 mg) and slow (6 hours) infusion of tissue-type plasminogen activator (t-PA) without bolus with repetition as needed as a first-line therapy have been reported to be the safest regimen compared with higher doses or faster infusions of t-PA or streptokinase. The overall success rate in the whole series was 83.2%; it did not differ significantly among Groups-I through V (68.8%, 85.4%, 75%, 81.5%, and 85.5%, respectively; *p* 0.46). The overall complication rate in the whole series was 18.6%. Although the overall complication rate was similar among Groups-I through IV (37.5%, 24.4 %, 33.3%, and 29.6%, respectively; *p* 0.05 for each comparison), it was significantly lower in Group V (10.5%, *p* 0.05 for each). The study concluded that low-dose slow infusion of t-PA repeated as needed without a bolus provides effective and safe thrombolysis in patients with prosthetic valve thrombosis[10]. In a study by Özkan et al, Ultraslow infusion (25hours) of low-dose (25mg) t-PA, was used in all patients a with PVT, with an overall success rate of 90% (95% CI 0.85-0.95) with low complications and mortality[11]. In another study in elderly patients prolonged and low dose infusions of thrombolytics showed an initial and cumulative success rates of 40.7% and 85.2%, respectively[12]. Wei et al studied a non-thrombolytic regimen based on clopidogrel plus warfarin with initial 5 days of LMWH resulted in recovery of normal valve function in 73% of patients with PVT and stable hemodynamics, after an average of 36.4 ± 23.1 days' observation[13].

Table-II: Outcome of thrombolytic therapy.

Outcome	NYHA I/II 21	NYHAIII/IV 29	*p*-value
Primary outcome Complete response	14 (66.66%)	10 (28.57%)	0.044
Secondary outcome	4 (19.04%)	11 (37.93%)	NS
Death	3 (14.28%)	10 (34.48%)	NS
CNS/non-CNS embolism	1 (4%)	1 (3.4%)	NS

Surgery versus thrombolytic therapy: In a meta-analysis and a systematic review by Castilho et al, surgery was compared with thrombolysis. There was a highly significant difference in mortality between the two groups: surgery, 18.1% (CI, 14.6-22.1%) and thrombolysis, 6.6% (CI, 4.8–9.9%) (p<0.001)[14]. In a literature survey by Huang et al, results revealed 30-day mortality in the group treated with surgery at 15% (98 deaths in 662 patients) vs. 8% (61 deaths in 756 patients) in the thrombolysis pooled. The rates of recurrence and complications, however, were higher in patients treated with thrombolysis[15].

CONCLUSION

PVT is a serious complication of prosthetic heart valves with high mortality and morbidity both due to disease and treatment. It is recommended that urgent surgery be carried out once failed fibrinolytic therapy is observed after 24 hours. Management requires a well-coordinated heart team approach not only to rapidly diagnose the condition but also to define the optimal treatment for the patient.

LIMITATION OF STUDY

Our study is limited due to lesser use of TEE, which is important not only in evaluation of valve function but also in quantification of thrombus size.

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CONFLICT OF INTEREST

This study has no conflict of interest to be declared by any author.

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