International Journal of Science and Research (IJSR)
ISSN: 2319-7064
ResearchGate Impact Factor (2018): 0.28 | SJIF (2018): 7.426

Prosthetic Valve Thrombosis: A Clinical, Echocardiographic and Cinefluoroscopic Study with Special Reference to Thrombolytic Therapy

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Abstract: ***Background: Prosthetic valve thrombosis (PVT) is a rare but serious complication of valve replacement, most often encountered with mechanical prostheses. The significant morbidity and mortality associated with this condition warrants rapid diagnostic evaluation. Transthoracic, TEE and Cinefluoroscopy represent the main diagnostic procedures. Methods: The present study is an institutional based single centre prospective and retrospective observational study conducted in patients who are admitted with diagnosis of prosthetic valve thrombosis to the Department Of Cardiology, Gandhi Medical college/Hospital, Secunderabad, Telangana, India. The study was conducted between April 2016 to February 2018. A total of 66 patients admitted to the department of cardiology with a diagnosis of prosthetic valve thrombosis. Results: A total of 66 patients included in this study had mean age of 35.2 ±10.5 years and 43(65.15%) are females and 23(34.85%) are males. 58(87.88%) patients underwent MVR, 4(6.06%) underwent AVR and 4(6.06%) underwent DVR. Thrombolytic agent used was streptokinase in 65 (98.48%) patients and 1(1.52%) received tenecteplase. The thrombolytic therapy was successful in 33(50%) patients, partially successful in 12(18.18%) and failure in 21(31.82%). In this study the overall success rate in 45(68.18%) patients. Among 66 patients, 4 patients not achieved clinical and hemodynamic improvement and 17 patients died. Complications during this study are 3 patients developed CVA because of embolism Conclusion: Prosthetic valve thrombosis is an urgent life threatening medical emergency, which warrants rapid diagnostic assessment. Thrombolytic therapy is an effective and easily available treatment modality which can be rapidly instituted in patient with prosthetic valve thrombosis.***

Keywords: Prosthetic Valve Thrombosis, Post Thrombolytic, Echocardiographic, Cinefluoroscopic

1. Introduction

Prosthetic valve thrombosis (PVT) is a rare but serious complication of valve replacement, most often encountered with mechanical prostheses. The significant morbidity and mortality associated with this condition warrants rapid diagnostic evaluation. However, diagnosis can be challenging, mainly because of variable clinical presentations and the degree of valvular obstruction. Cinefluoroscopy (for mechanical valves) and transthoracic and transesophageal echocardiography(TEE) represent the main diagnostic procedures.

In cases of obstructive PVT, optimal treatment remains controversial[1]. The different therapeutic modalities available for PVT (anticoagulant treatment, fibrinolysis, surgery) will be largely influenced by the presence of valvular obstruction, by valve location (left- or right-sided), and by clinical status. Hence, treatment of an obstructive left-sided PVT will differ from that of non-obstructive or right-sided PVT. The present study intended to reevaluate the diagnostic and therapeutic approach to a patient presenting with PVT.

2. Methods

This study is an institutional based single centre prospective and retrospective observational study conducted in the consecutive patients who are admitted with diagnosis of prosthetic valve thrombosis to the Department Of Cardiology, Gandhi Medical college/Hospital, Secunderabad, Telangana, India. The study was conducted between April 2016 to February 2018. Study was reviewed and approved by the institutional ethical committee, Gandhi medical college, secunderabad. Study population includes 66 patients admitted to the department of cardiology with a diagnosis of prosthetic valve thrombosis during the time period

Inclusion criteria

1) Patients who presented with diagnosis of prosthetic valve thrombosis.
2) All age groups are included.
3) Both male and female patients are included

Exclusion criteria

1) Patients with contraindications for thrombolysis are excluded.
2) Patients who directly underwent surgery to PVT.
3) Patients who refused thrombolysis

All the patients were assessed clinically, blood samples were collected for routine investigations and PT/INR estimation, TTE was done at baseline 24 hr, 48hr, 72hr and 96 hr. Eligible patients underwent TEE and cinefluroscopy Echo was done with Phillips IE 33 machine and cinefluroscopy done with Siemens artis zee machine. Informed consent was taken.

Thrombolytic treatment protocol

Inj.streptokinase loading dose of 2.5 lac units followed by 1 lac per hr as infusion for next 24 hr. Once target gradients are achieved patients are later maintained with anticoagulants.

For Tenecteplase a bolus regimen was followed depending on weight.

Evaluation of efficacy

Efficacy of TLT was evaluated from the clinical data and the TTE and cinefluoroscopic findings. Clinical improvement is defined as at least 2 functional class improvement, absence of orthopnoea and PND, vital parameters like blood

pressure, heart rate and respiratory rate are normalized. Haemodynamic improvement is defined as normalization of pressure gradients across valve and leaflet mobility (echo and cinefluoroscopy)

Success is defined as:

1) Successful: Clinical and hemodynamic normalization confirmed by cinefluoroscopy (normal mobility of tilting disks) or TTE/ TEE data (normalization of transprosthetic gradient and normal mobility of leaflet).
2) Partially successful: significant clinical improvement without complete recovery of disc or leaflet motion on fluoroscopy and/or TTE.
3) Failure: no clinical improvement, in many cases associated with death or complications.
4) In some cases, TLT succeeded in hemodynamic terms, but failed because of severe complications. These patients were classified as success with complications.
5) Overall success is defined as the total of successful and partially successful

Statistical analysis

Statistical analysis is done with SPSS software. Means are compared with paired t-test and for categorical variables frequency and chi square test is used. Analysis was done only for significant frequencies.

3. Results

Basic demography

A total of 66 patients included in this study had mean age of 35.2 ±10.5 years and 43(65.15%) are females and 23(34.85%) are males with ratio of M:F =1:1.86. 58(87.88%)patients underwent MVR, 4(6.06%) underwent AVR and 4(6.06%) underwent DVR. 37(56.06%)patients are mitral position TTK chitra valves, 22(33.34%) are mitral position SJM valves, 2(3.03%) are aortic position TTK chitra valves and 5(7.57%) are aortic position SJM valves.

Clinical Status

Among 66 patients, 3 (4.55%) are in dyspnea, functional class II, 26 (39.39%) are in dyspnea, functional class III, 37 (56.06%) are in dyspnea, functional class IV and 4(21.21%) patients presented with hypotension.

Anticoagulation and Thrombolytic Agent

Among 66 patients only 22.73 %(15) had compliance to anticoagulant at the time of presentation and 96.97 %(64) are not in therapeutic range of anticoagulation, only 3.03 %(2) have adequate anticoagulation. Out of 66 patients 98.48 %(65) received streptokinase and 1.52 %(1) received tenecteplase as thrombolytic agent

Transthoracic Echocardiography

At mitral position before thrombolysis maximum PPG is 60mmHg and minimum is 21mmHg and MPG is 42 and 15 mmHg. At mitral position after thrombolysis maximum PPG is 24mmHg and minimum is 4mmHg and MPG is 18mmHg and 2mmHg.

There is statistically significant difference of PPG at mitral position before and after TLT. PPG before TLT is 39.37±9.19 mmHg and after thrombolysis its 12.02±6.51mmHg with p value of <0.0001.There is statistically significant difference of MPG at mitral position before and after TLT. MPG before TLT is 26.00±6.13 mmHg and after thrombolysis its 6.06±4.95 mmHg with p value of <0.0001(Table 1)

At aortic position before thrombolysis maximum PPG is 141mmHg and minimum is 65 mmHg and MPG is 77mmHg and 30 mmHg. At aortic position after thrombolysis maximum PPG is 106mmHg and minimum is 26mmHg and MPG is 64mmHg and 15mmHg.

There is statistically significant difference of PPG at aortic position before and after TLT. PPG before TLT is 104.57±32.38 mmHg and after thrombolysis its 50.75±37.74mmHg with p value of 0.003.There is statistically significant difference of MPG at aortic position before and after TLT. MPG before TLT is 62±24.6 mmHg and after thrombolysis its 31±23.1 mmHg with p value of 0.007. (Table 2).

Transesophageal Echocardiography

TEE showed visible thrombus in 6 patients out of 26 patients in mitral position before TLT. With minimum size of 0.7cm^2 and maximum size of 1.4 cm^2. No visible thrombus seen in aortic position of 2 before TLT. No thrombus is seen after thrombolysis in both positions (n-49)

Cinefluoroscopy

There is statistically significant difference between opening angle, closing angle and leaflet excursion before and after thrombolytic therapy in SJM valve at mitral.

Correlatoin between echo pressure gradients and cinefluroscopy leaflet excursion of SJM valve at mitral position

PPG and MPG are mildly negative correlated with leaflet excursion with r value of -0.13 and -0.26 respectively before thrombolysis at mitral position.

PPG and MPG are moderately negative correlated with leaflet excursion with r value of -0.42 and -0.49 respectively after thrombolysis at mitral position.

Outcome of Thrombolytic Therapy

The thrombolytic therapy was successful in 33(50%), partially successful in 12(18.18%) and failure in 21(31.82%). The overall success is in 45(68.18%) patients. Among 59 patients who had thrombosed valve at mitral position, TLT was successful in 31(53.54%) patients, partially successful in 11(18.64%) and failed in 17(28.82%) patients with overall success in 42(71.18%).

Outcome at Mitral Position based on Valve Type

At mitral position, among 37 patients with TTK Chitra valve TLT is successful in 15(40.54%), partially successful in 6(16.22%) and failed in 16 (43.24%) with overall success in 21(56.76%) patients whereas 22 patients with SJM valve 16(72.73%) had successful, 5(22.73%) had partially successful and 1(4.54%) had failure. TLT with overall success in 21(95.46%) patients. There is statistically significant difference of overall success at mitral position between SJM and TTK Chitra valve with better result with SJM valve (p-value 0.006).

Outcome at Aortic Position

Among 7 patients who had thrombosed valve at aortic position, TLT was successful in 2(28.58%) patients, partially successful in 1(14.28%) and failed in 4(57.14%) patients with overall success in 3(42.86%)

Outcome of TLT at Aortic Position based on Valve Type

At aortic position, among 2 patients with chitra valve TLT 1(50%) is successful and 1(50) is failure with overall success in 1(50%) patient whereas 5 patients with SJM valve 1(20%) is successful, 1(20%) is partially successful and 3(60%) had failure TLT with overall success in 2(40%) patients

Outcome of TLT Compared Mitral to Aortic Position

At mitral position the overall success is 42(71.18%) of 59 patients whereas at aortic position the overall success is 3(42.86%) out of 7 patients. At mitral position no of patients expired is 14(23.72%) of 59 patients whereas at aortic position the no of patients expired is 3(42.86%) out of 7 patients.

There is no statistically significant difference between mitral and aortic positions in terms of overall success (p=0.07) and death (p = 0.23).

Outcome of TLT Compared SJM to TTK

Overall success with TLT is 22(56.71%) with TTK Chitra valve whereas with SJM valve it is 23(85.19%) there is statistically significant difference (p = 0.01) Mortality in SJM valve group is 2(7.41%) and TTK Chitra valve group is 15(61.54%) there is statistically significant difference (p=0.003)

Outcome of TLT Compared SJM to TTK Chitra at Mitral Position

Overall success with TLT is 21(56.76%) with TTK Chitra valve whereas with SJM valve it is 21(95.45%) there is statistically significant difference (p = 0.001) at mitral position. There are no deaths in SJM valve group and TTK Chitra valve group is 14(37.84%) there is statistically significant difference (p=0.01).

Table 1: (Trans thoracic echocardiography pressure gradients at mitral position before and after thrombolysis)

Thrombolysis (TLT)	Peak pressure gradient (PPG) mm of hg	Mean pressure gradient (MPG) mm of hg	p value
Pre TLT (n-59)	60	42	< 0.0001
Post TLT (n-46)	24	18	<0.0001

Table 2: (Trans thoracic echocardiography pressure gradients at aortic position before and after thrombolysis)

Thrombolysis (TLT)	Peak pressure gradient (PPG) mm of hg	Mean pressure gradient (MPG) mm of hg	p value
Pre TLT (n-7)	141	77	0.003
Post TLT (n-4)	106	64	0.007

Mortality

Among 66 patients who received thrombolytic therapy 17(25.75%) patients died. Among the 17 patients died, 14(82.34%) underwent MVR, 1(5.9%) AVR and 2(11.76%) DVR. Of 2 DVR patients both has aortic valve thrombosed. Total patients died in aortic position PVT are 3(17.66%). Of 17 patients 16(94.1%) are in NYHA class IV and 1(5.9%) is in class III. 11(64.71%) are in cardiogenic shock. None of the patients has therapeutic INR.

Complications

3 patients developed CVA because of embolism. Of which 1 patient died because of large infarct. 1 patient developed seizures after bolus infusion of streptokinase. None of the patient has Major bleeding complications.

4. Discussion

Thrombosis is a serious complication of prosthetic heart valve replacement and incurs a high mortality. Early diagnosis of obstructive thrombosis is paramount in optimizing management. In cases of obstructive PVT, optimal treatment remains controversial[1]. The different therapeutic modalities available for PVT (anticoagulant treatment, fibrinolysis, surgery) will be largely influenced by the presence of valvular obstruction, by valve location (left- or right-sided), and by clinical status. Hence, treatment of an obstructive left-sided PVT will differ from that of non-obstructive or right-sided PVT.

This is an observational prospective and retrospective study. We report here a single-center study of 66 instances of PVT treated with thrombolysis. The efficacy of TLT was assessed by well-established hemodynamic parameters derived from echocardiographic and cinefluoroscopic examinations as well as by clinical evaluation.

Out of 66 patients analyzed in this study 43(65.15%) are females, 23(34.85%) are males {Ratio (M: F) =1:1.86}. Mean age of the study group is 35.2 ±10.5 years the mean age of International PRO-TEE Registry[2] is 54.2 ±15.8 and in an RCT trial by Karthikeyan *et al*[3] in conventional infusion group it is 31±10. The mean age of the male population is 37.00±11.04 and that of the female population is 34.18±10.19.

The main clinical presentation is dyspnea (100%) and hypotension(21.21%). Most of the patients, 37(56.06%), are in NYHA class IV functional status in our study. Where as in PRO TEE Registry it is 19(17.7%) in Karthikeyan *et al* study it is 7(12%). In the study group only 2(3.03%) patients have therapeutic INR whereas 64(96.97%) are not in therapeutic range of anticoagulation. Of whom only 15(22.73%) had compliance to anticoagulant at the time of

presentation 51(77.27%) are not. In PRO-TEE REGISTRY group 33(32.4%) are in therapeutic INR and 99(93.4%) are using anticoagulant.

Thrombolytic agent used was streptokinase in 65 (98.48%) and 1(1.52%) received tenecteplase as the patient had recent history of administration of streptokinase. In PRO TEE REGISTRY group streptokinase was used in 58(54.7%), t-PA in 31(28.9%) and urokinase in 18(17%) patients.

There is statistically significant difference between pre TLT valve gradients and post TLT gradients in TTE. There is statistically significant difference between opening angle, closing angle and leaflet excursion before and after thrombolytic therapy in SJM valve at mitral position in fluoroscopy.

PPG and MPG are mildly negative correlated with leaflet excursion with r value of -0.13 and -0.26 respectively before thrombolysis at mitral position.

PPG and MPG are moderately negative correlated with leaflet excursion with r value of -0.42 and -0.49 respectively after thrombolysis at mitral position.

The thrombolytic therapy was successful in 33(50%), partially successful in 12(18.18%) and failure in 21(31.82%). The overall success is in 45(68.18%) patients in the entire study group. The clinical success in PRO-TEE registry group is in 79 patients (73.8%) and complete clinical response in Karthekayan *et al* study in conventional infusion group is in 32(53.33%) patients. Our study has success rate similar to these studies despite of having high number of patients in functional class IV 37(56.06%) where as in pro TEE Registry it is 19(17.7%) in Karthikeyan *et al* study it is 7(12%).

Among 66patients 4patients not achieved clinical and haemodynamic improvement and 17patients died. Among the 17 patients died 14(82.34%) underwent MVR, 1(5.9%) AVR and 2(11.76%) DVR. Of 2 DVR patients both has aortic valve thrombosed. Total patients died in aortic position PVT is 3(17.66%). Of 17 patients 16(94.1%) are in NYHA class IV and 1(5.9%) is in class III. 11(64.71%) are in cardiogenic shock. None of the patients has therapeutic INR.

In Karthikeyan et al study mortality is in 4(7%). When SJM valve group alone is considered the mortality in our study is 2(7.41%). Poor clinical status at time of presentation (higher functional class and cardiogenic shock), delayed presentation and varied valve composition may be the probable cause of mortality.
The other complications seen in our study is 3(4.54%) patients developed CVA because of embolism. Of which 1 patient died because of large infarct.1 patient developed seizures after bolus infusion of streptokinase. None of the patient has Major bleeding complications. In Karthikeyan *et al* study the conventional infusion group has 2(3%) patients embolic stroke or non-CNS embolic event and 4 patients has major bleeding.

Our study has shown that patients presenting with PVT have dyspnea as common presentation, has INR in sub therapeutic levels, non-compliant to anticoagulants, elevated transvalvular gradients in echo reduced leaflet excursion in cinefluoroscopy with significant reduction of gradients and improvement of leaflet excursion with TLT. The outcome doesn't vary with position of valve i;e aortic or mitral. Outcome varies with type of valve i;e better with SJM valve when compared with TTK Chitra valve both in success and mortality.

- Sharma and Mewada[4] in 2010 studied 48 patients with STK 250000iu followed by 100000IU/hr clinical success was seen in 81% and failure in 10% mortality in 6%.
- Roudat *et al*[5]130 patients from 1978 to 2001 with different thrombolytic ages showed clinical success in 86% in STK group with failure in 11.8% and death in 11.8%.
- Gupta *et al*[6] analysed 110 patients from 1990 to 1999 with STK as thrombolytic agent showed success in 81.8% failure in 8.2% and mortality in 7.3%
- Manteiga *et al*[7] in 1998 studied rapid infusion of STK 1.5MU over 90 min showed success in 59% failure in 27% and mortality in 4.5%
- Reddy *et al*[8] in 1990 :1993 studied 44 patients with low dose slow infusion STK showed clinical success in88.6%, failue in 11.4% and mortality in 4.5%
- Ozkan *etal*[9] in 1993 :1997 studied 16 patients with PVT who underwent STK infusion of 1.5 MU over 3hr showed a clinical success of 68.8% and mortality of 12.5%
- Ozkan *et al*[9] in 2001 :2002 studied TPA (10mg bolus 90 mg over 5 hr) in 12 patients of PVT showed success in 75% and mortality in 16.7 %
- Teshima *e ta1*[10] in 1998 :2001 studied 27 patients with TPA showed success in 55.6% and failure in 22.2 %

When compared with these studies the SJM group of our study, with a success rate of 85.19%, failure rate of 14.81% and death rate of 2(7.41%), have similar or better results

5. Limitations of the Study

- This study is a single center study and so applicability of the findings to wider variety of patients is in doubt.
- Due to the observational nature of the study, it is impossible to confirm causality.
- Also, we were unable to rule out residual measured and unmeasured confounding factors that may result in different outcomes.

6. Conclusions

- Prosthetic valve thrombosis is an urgent life threatening medical emergency, which warrants rapid diagnostic assessment.
- Diagnosis of prosthetic valve thrombosis can be made with reasonable accuracy by mode of presentation, clinical examination, transthoracic echocardiography and cinefluoroscopy.
- Noncompliance of anticoagulant with subtherapeutic INR is a risk factor for development of prosthetic valve thrombosis.

- Cinefluoroscopy is of great value in diagnosis of prosthetic valve thrombosis in patients with St. Jude medical valve.
- Cinefluoroscopy has no role in diagnosis of prosthetic valve thrombosis in patients with TTK Chitra valve (radiolucent).
- Thrombolytic therapy is an effective and easily available treatment modality which can be rapidly instituted in patient with prosthetic valve thrombosis which is a critical life threatening medical emergency.
- Outcomes of Thrombolytic therapy are better in St. Jude medical valve when compared with TTK Chitra valve.
- Administration of streptokinase by conventional regimens is lifesaving in patients presenting with acute severe pulmonary edema.
- Newer oral anticoagulants such as thrombin and factor Xa antagonists, which do not require routine laboratory monitoring, may be candidates for evaluatuion in patients with mechanical valves

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