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Recurrent Prosthetic Valve Thrombosis: Fibrinolytic Treatment for Recurrent Left Sided Prosthetic Valve Thrombosis

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Abstract

Background: *Prosthetic valve thrombosis is a devastating complication of valve replacement therapy. Many patients experience recurrent prosthetic valve thrombosis which is accompanied by increased morbidity or mortality. The Recurrent PVT (Prosthetic valve thrombosis) can be managed either by surgery or by repeat thrombolysis. Redo surgery carries with it more mortality and morbidity. There has been no large studies which evaluated the efficacy of re-thrombolysis in recurrent PVT.*

Objectives of the study were.

1) To assess the efficacy of thrombolysis in recurrent PVT

2) To assess the relationship of different patient variables responsible for successful thrombolysis.

3) To know the factors associated with recurrent prosthetic valve thrombosis.

Materials and methods: *This is a retrospective study. All the patients admitted at our institute with recurrent prosthetic valve thrombosis from Jan 2011 to Dec 2014 are included in the study. A total of 32 patients had recurrent PVT, all patients received thrombolysis according to the prespecified protocol. The effectiveness of the thrombolysis was analysed with serial echocardiography.*

Results: *Mean age of the patients was 41.15±10.96 years. 17(53.1%) patients were females. Median duration following valve replacement was two years. 21(43.8%) patients had bileaflet prosthetic valve and 18(56.3%) were having tilting disc prosthetic valve. Only one patient presented with NYHA class I symptoms. Baseline echocardiography demonstrated peak and mean mitral gradients of 34.30±6.07 and 21.34±6.22 mmHg respectively. Whereas aortic prosthetic valve peak and mean gradients were 100.2±31.33 and 59.1±25.1 mmHg respectively. The mean left ventricle ejection fraction was 49.66±12.21%. Majority of the patients 21(65.6%) had normal or more than normal INR valve at the time of presentation. Neutrophil to lymphocyte ratio was significantly associated with the number of times patient was admitted with recurrent prosthetic valve thrombosis. At mitral position there were total 26 incidences of prosthetic valve thrombosis of which 16 (61%) patients had full response, 4(15.3%) and 6(23.0%) prosthetic valve thrombosis had incomplete and failed thrombolysis. In aortic position a total of 9 incidents of thrombosis were noted and all of these patients recovered completely following thrombolysis. There were two deaths and three embolic cerebral infarcts post thrombolysis, these events occurred in prosthetic valve thrombosis at mitral valve position and in NYHA class 4 patients. Urokinase and streptokinase had similar efficacy in the treatment of prosthetic valve thrombosis.*

Conclusion: *Recurrent prosthetic valve thrombosis can be treated with thrombolysis with good results. Neutrophil to lymphocyte ratio was significantly associated with number of times patient admitted with recurrent PVT. Patients presenting with NYHA class IV have higher mortality and failed of thrombolysis. Recurrent PVT at mitral position had a higher failure compared to aortic position.*

Introduction

PVT is fatal complication of prosthetic valve replacement surgery.PVT occurs with a incidence of 0.3-1.% in spite of improvements in the type of artificial valve and the treatment protocol patient education and adequate anticoagulation.[1] Thromboembolic complications, including systemic emboli, are more frequent and occur at a rate of 0.7–6% patient years. Prosthetic valve thrombosis has been divided into two types, Obstructive Prosthetic Valve Thrombosis (OPVT) and Non-Obstructive Prosthetic Valve Thrombosis (NOPVT). Both OPVT and NOPVT can present with systemic thromboembolism and heart failure, but it may be asymptomatic. Trans-Esophageal Echocardiography has emerged as the technique of choice for diagnosis and management. There are three treatment options; surgery, thrombolysis and anticoagulation The different therapeutic modalities available for PVT will be largely influenced by the presence of valvular obstruction, by valve location (left- or right-sided), and by clinical status. Many patients have repeated PVT. Recurrence was noted in 18.9% with a mean interval of 2.06 years [2]. Ideal therapy for the recurrent PVT remains controversial.[3-6]. Thrombectomy or valve replacement is the conventional treatment for this condition, with an associated mortality rate ranging from 4.7% to 20%. Thrombolysis is emerging as a promising alternative to surgery, particularly in critically ill patients, with a success rate ranging from 75% to 83 %.[7]

High mortality and costs associated with redo surgery favours thrombolysis as an attractive treatment modality. The recent review by Lengyel et al. [8] of 200 published reports of left-sided prosthetic heart valve thrombolysis showed an 82% initial success rate, an overall thromboembolic rate of 12%, and a mortality rate of 10%. Success rate for thrombolysis in recurrent prosthetic valve thrombosis has been shown to be 75%. There are no clear-cut guidelines for the management of recurrent prosthetic valve thrombosis.

The objectives of the present study are

1) To assess the efficacy of thrombolysis In recurrent PVT

2) To assess the variables that predispose to recurrent PVT

3) To establish a relationship of different patient variables with response to thrombolysis.

Materials and methods

It is a retrospective study between Jan 2011 and Dec 2014, a total of 32 patients admitted in our centre with recurrent PVT. During this period, our policy has been to routinely use thrombolysis as the treatment modality for PVT. All patients with a confirmed diagnosis of obstructive PVT on fluoroscopic or echocardiographic criteria and with absence of any contraindications to thrombolysis were included. All patients were

treated with streptokinase (STK) or urokinase (UK) 2,00,000 U bolus over 30 minutes followed by an infusion of 100,000 U/h . Close monitoring for clinical, echocardiographic, and cinefluoroscopic markers of success and a constant vigil for complications was maintained throughout the infusion. transthoracic echocardiography (TTE) with Doppler imaging was performed at 0, 24, 48, and 72 hours during the infusion.

The infusion was terminated at any such time when either (1) the improvement in clinical status was corroborated by objective evidence of complete recovery on Doppler echocardiography and cinefluoroscopy or if (2) an intracranial haemorrhage or a major haemorrhage (needing blood transfusion) occurred. The infusion was stopped at 72 hours even in the absence of complete response.

After cessation of thrombolysis, heparin infusion was started to maintain the activated partial thromboplastin time (APTT) between 2 and 2.5 times control. Oral anticoagulation was started concurrently and when the international normalized ratio/prothrombin time (INR/PT) had increased to 2.5 to 3 times control, and after that heparin was discontinued.

Diagnostic criteria

The clinical suspicion of PVT was confirmed by complementary investigations [Trans thoracic Echo (TTE), Trans oesophageal Echo (TEE), cinefluoroscopy] in all patients. Doppler trans thoracic echocardiography (TTE) is usually performed in all patients, sometimes backed up by TEE, if the valves are radio opaque cinefluoroscopy was used.

Evaluation of efficacy

Efficacy of fibrinolysis was evaluated from the clinical data and the TTE and cinefluoroscopic findings. Although we usually observed a rapid improvement in clinical status, fibrinolysis was continued until the TTE and/or cinefluoroscopic data became normal. We defined success as:

1. Full: Hemodynamic normalization which was confirmed by cine- fluoroscopy (normal mobility of disks) or TTE/ TEE data (normalization of transprosthetic gradient, normal mobility of leaflet).
2. Incomplete: 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.

Statistical Methods: Descriptive and inferential statistical analysis has been carried out in the present study. Results on continuous measurements are presented on Mean ± SD (Min-Max) and results on categorical measurements are presented in Number (%). Significance is assessed at 5 % level of significance. The following assumptions on data are made, Assumptions: 1.Dependent variables should be normally distributed, 2.Samples drawn from the population should be random, Cases of the samples should be independent. Analysis of variance (ANOVA) has been used to find the significance of study parameters between three or more groups of patients, Student t test (two tailed, independent)

has been used to find the significance of study parameters on continuous scale between two groups (Inter group analysis) on metric parameters. Chi-square/ Fisher Exact test has been used to find the significance of study parameters on categorical scale between two or more groups.

Statistical software: The Statistical software namely SPSS 15.0 was used for the analysis of the data and Microsoft word and Excel have been used to generate graphs, tables etc**.**

Results

Mean age of the patients was 41.15 ±10.96 years, 17(53.1%) patients were females. Median duration folowing valve replacement was two years, with mitral valve replacement being more than (71.9%) the aortic valve replacement(18.8%). 21(43.8%) patients had bi-leaflet prosthetic valve and 18(56.3%) were having tilting disc prosthetic valve. Only one patient presented with NYHA class I symptoms. Whereas 8(25%), 9(28%) and 14(43.8%) patients presented with NYHA class II, III and IV respectively**.** Baseline echocardiography demonstrated peak and mean mitral gradients of 34.30±6.07 and 21.34±6.22 mmHg respectively. Whereas aortic prosthetic valve peak and mean gradients were 100.2±31.33 and 59.1±25.1 mmHg respectively. Three (9.4%), twelve (37.5%) and seventeen (53.1%) patients had ejection fraction of <30%, 30-50% and >50% respectively with a mean left ventricle ejection fraction of 49.66±12.21%. Majority of the patients were compliant with the medications (71.9%). Only 11 (34.3%) patients were non compliant with anticoagulants. Majority of the patients 21(65.6%) had normal or more than normal INR valve at the time of presentation. All the patients studied had Rh +ve blood group. Majority of the patients were having blood group of A+ve (40.6%). Patients belonging to AB +ve and O+ve were 5(15.6%) and 6(18.8%) respectively (see table 4). Mean gradient was higher in patients with low INR value (<2) than those with INR of >2 which was statistically significant (see table 2). Majority of the patients with prosthetic valve had Saint Jude bileaflet Valve thrombosis (see table 3). NYHA class at presentation was not significantly associated with past history of prosthetic valve thrombosis or number of times patient had PVT (see table5). Neutrophil to lymphocyte ratio was significantly associated with the number of times patient was admitted with recurrent prosthetic valve thrombosis (see table 6).

Results of thrombolysis

In mitral position there were total 26 episodes of prosthetic valve thrombosis of which 16 (61%) patients had full response, 4(15.3%) and 6(23.0%) prosthetic valve thrombosis had incomplete and failure following thrombolysis. In aortic position a total of 9 incidents of thrombosis were noted and all of these patients recovered completely following thrombolysis. There were two deaths and three embolic cerebral infarcts post thrombolysis, these events occurred in prosthetic valve thrombosis at mitral valve position (see table 8). The decline in peak and mean gradient both in mitral and aortic position was more in patients presented with NYHA class 1or 2 than those presenting with NYHA class 3 or 4 which was statistically significant (see table 7). There

was no significant asscociation of therapeutic INR value and complication rate (see table 9). All the complications and failure to thrombolysis and death occurred in NYHA class 4 patients (see table 10). Univariate analysis of different patient variables with successful thrombolysis was assessed in which except for baseline peak aortic prosthetic gradient none of the variables had any significant association (see table 12). Urokinase and streptokinase had similar efficacy in the treatment of prosthetic valve thrombosis.

Table 1: Number of years following valve replacement surgery in recurrent prosthetic valve thrombosis patients.

Duration	No. of patients	%
≤1 years	7	21.9
1-2 years	10	31.3
2-5 years	7	21.9
>5 years	8	25.0
Total	32	100.0

Table 2: Mean and Peak Gradient according to INR

	INR		Total	P value
	<2	>2		
Peak Gradient	35.18±6.03	33.67±6.24	34.31±6.08	0.541
Mean Gradient	24.00±5.00	19.40±6.47	21.35±6.23	0.061+

Table 3: Distribution of different mechanical prosthetic valves in patients presented with recurrent PVT

Valve name	No. of patients	%
SJ	14	43.8
TTK	9	28.1
ATS	7	21.9
OMN	1	3.1
SOR	1	3.1
Total	32	100.0

Table 4: Baseline characteristics of the recurrent prosthetic valve thrombosis patients (n=32)

Mean age (years [range])	41.15±10.96 [19-63]
Sex (male/female [%])	15(49.6) /17(53.1)
Median time since valve replacement years (range)	2.0 (1.26-7.25)
Position of Prosthetic valve thrombosis (%)	
Mitral	23(71.9)
Aortic	6(18.8)
Dual	3(9.4)
Type of prosthetic valve	
Bileaflet	14(43.8)
Tilting disk	18(56.3)
Oral anticoagulation status (%)	
Therapeutic INR*	21(65.6)
Subtherapeutic INR (< 2)	11(34.4)
NYHA class at presentation (%)	
I	1(3.1)
II	8(25)
III	9(28.1)
IV	14(43.8)
Baseline echo data	
Transvalvular gradients (mm Hg)	
Mitral (n=26)	
Peak Gradient	34.30±6.07
Mean Gradient	21.34±6.22
Aortic (n =9)	
Peak Gradient	100.2±31.33
Mean gradient	59.1±25.1
EF(%)	
<30	3(9.4)
30-50	12(37.5)
>50	17(53.1)
Complaiance Yes/No	23(71.9)/9(28.1)
Eosinophil count <6% />6%	21/11
N/L ratio	
<2	6(18.8%)
2-3	9(28.1%)
>3	17(53.1%)
Blood group n(%)	
A+	13(40.6)
B+	8(25)
AB+	5(15.6)
O+	6(18.8)

Table 5: Correlation of NYHA class at presentation with number of times patient had recurrent PVT

NYHA	Past PVT				Total
	1	2	3	4	
1	1(4.5%)	0(0%)	0(0%)	0(0%)	1(3.1%)
2	5(22.7%)	2(33.3%)	1(50%)	0(0%)	8(25%)
3	7(31.8%)	0(0%)	1(50%)	1(50%)	9(28.1%)
4	9(40.9%)	4(66.7%)	0(0%)	1(50%)	14(43.8%)
Total	22(100%)	6(100%)	2(100%)	2(100%)	32(100%)

P=0.582, Not significant, Fisher Exact test, PVT = prosthetic valve thrombosis

Table 6: Correlation of Neutrophil to lymphocyte Ratio with number of times of recurrent PVT

NL Ratio	Past PVT				Total
	1	2	3	4	
≤2	3(13.6%)	2(33.3%)	1(50%)	0(0%)	6(18.8%)
2-3	4(18.2%)	3(50%)	1(50%)	1(50%)	9(28.1%)
>3	15(68.2%)	1(16.7%)	0(0%)	1(50%)	17(53.1%)
Total	22(100%)	6(100%)	2(100%)	2(100%)	32(100%)

P=0.065+, Significant, Fisher Exact test, PVT = prosthetic valve thrombosis.

NL= Neutrophil to lymphocyte ratio

Table 7: Efficacy of thrombolytic therapy according to NYHA class at presentation

	NYHA class 1or 2	NYHA class 3	NYHA class 4	P value
Successful	6	8	8	
Failure	3	1	6	
Decline in mitral Peak gradient	18.5±8.85(n=4)	22.62±7.0(n= 8)	16.21±8.01 (n=14)	0.006
Decline in mitral mean gradient	16.5±10.75	14.5±5.6	11.57±6.83	0.067
Decline in aortic peak gradient	78.8±27.41(n=5)	64.33±17.78(n=2)	75(n=1)	-
Decline in aortic mean gradient	54.8±27.68	39±11.53	30	-

Table 8: Results of thrombolytic therapy

Extent of response	**N**
Complete	
Mitral	16(61%)
Aortic	9(100%)
Partial (n=6)	
Mitral	4(15.3%)
Aortic	0
Failure (n=2)	
Mitral	6(23.0%)
Aortic	0
Clinical failure (n =4)	
Deaths	2
CVA	3
Surgery	1

Table 9: INR in association with complications

INR	**Complications**		**Total**
	No	**Yes**	
<2	11(39.3%)	0(0%)	11(34.4%)
>2	17(60.7%)	4(100%)	21(65.6%)
Total	28(100%)	4(100%)	32(100%)

P=0.272, Not significant, Fisher Exact test

Table 10: NYHA class and its association with complications

NYHA	**Complications**		**Total**
	No	**Yes**	
1	1(3.6%)	0(0%)	1(3.1%)
2	8(28.6%)	0(0%)	8(25%)
3	9(32.1%)	0(0%)	9(28.1%)
4	10(35.7%)	4(100%)	14(43.8%)
Total	28(100%)	4(100%)	32(100%)

P=0.185, Not significant, Fisher Exact test

Table 11: Complications of Thrombolysis

Embolism	
CVA	3
TIA	0
Peripheral	2
AMI	nil
Haemorrhage	
Major	nil
Minor	1
Deaths	
Cardiogenic shok	1
Embolic CVA	1
Hemorrhagic	-
Total	2
Redo surgery	1

TIA, Transient ischemic attack.
*Major embolic episodes: resulting in incomplete recovery at discharge or those needing therapeutic intervention.
†Major hemorrhage: requiring blood transfusion

Table12: Relationship of different patient variables with response to successful thrombolysis

	Univariate analysis			
Variable	χ^2	P value	OR(Success)	95% CI
Age <42/>42 years	0.582	0.446	0.55	0.12-2.54
Sex	1.006	0.316	2.17	0.10-2.12
NYHA class	0.0253	0.874	1.14	0.22-5.93
Base line MV peak Gradient	1.473	0.159	1.11	0.95-1.29
Base line peak Aortic gradient	2.458	0.037*	1.20	1.01-1.43
Type of valve §	1.561	0.212	0.38	0.08-1.77
Position of Valve ¥	0.731	0.393	0.38	0.04-3.75
Blood group £	0.731	0.393	2.64	0.27-26.24
Eosinophil count €	1.015	0.314	0.44	0.08-2.21
Past PVT ∞	0.518	0.472	0.56	0.12-2.72
N/ L ratio <2/ >2	0.015	0.903	0.89	0.13-5.88
EF <50 v/s >50	3.057	0.080	6.23	0.67-58.17
SK v/s UK	1.745	0.186	0.33	0.06-1.76

§Analyzed as bileaflet valve versus tilting disc valve.
¥ Analyzed as mitral versus aortic position.
€ eosinophil count <6% v/s >6%
£ O blood group v/s non O blood group.
∞ past prosthetic valve thrombosis episodes <2 v/s >2
N/L Neutrophil /lymphocyte ratio, EF- ejection fraction
SK- streptokinase, UK - urokinase
+ Suggestive significance (P value: 0.05<P<0.10)
*Moderately significant (P value:0.01<P ≤ 0.05)

Discussion

Thrombolysis for a recurrent episode of PVT is not as effective as it is for the first episode and causes more undesirable events. These patients have a greater tendency for repeated PVT after thrombolysis than when managed by thrombectomy (8%) or valve replacement (3%). It may be because of incomplete removal of all of the thrombus from the valve after thrombolysis, resulting in persistent abnormal flow acting as a substrate for subsequent episodes of thrombosis. Current methods of assessment of restoration of valve function might not be sensitive enough to detect this minor residual thrombus. The accelerated pannus formation on valves treated by thrombolysis may be another explanation for their tendency for recurrent PVT. This appears more implausible as most of our patients had short duration of symptoms before presentation (median 3 days, range 2–14 days). Previous data from studies advocate that duration of symptoms at presentation of less than one month favours thrombosis rather than pannus formation.[9] Increased thrombus burden in these predisposed valves might also explain the higher embolic stroke rate with thrombolysis in these patients. In the setting of recurrent prosthetic heart valve thrombosis or failure of streptokinase treatment, Urokinase and Tissue plasminogen have been used with safety and success.[10] Our study also did not show any difference in response to thrombolysis between streptokinase and urokinase. Studies have shown that success rate has been significantly higher with non-obstructive as compared with obstructive thrombi (75% vs. 40 %).[11] All of our patients were presented with obstructive form of prosthetic valve thrombosis. The immediate efficacy i.e. complete response was better for thrombosed aortic prosthesis than with the mitral prosthesis (100% versus 61%). Streptokinase, a widely used thrombolytic agent has a disadvantage of serious allergic reaction due to antibody formation against its antigenic structural foci. The relationship between antibodies and an immune reaction occurring after treatment with streptokinase is well known and may cause clinical failure of activation of fibrinolytic system by streptokinase especially in those with high serum titers of anti-streptokinase antibody [12]. For this reason second dose of streptokinase is not warranted within six months of prior administration. Antibodies may persist in serum for up to four years so, if thrombolysis is required during this period, another drug e.g. antihistamine or pre treatment with neutralizing antibody, have to be used to avert hypersensitivity reaction, though it is absolutely contra indicated within six months. In developing countries streptokinase may be the first choice for thrombolysis in mechanical valve thrombosis because of cost factor and availability. Nevertheless, because of its antigenicity, streptokinase may be associated with serious anaphylactic reaction in very sick patients with recurrent prosthetic valve thrombosis who have been treated with streptokinase in the recent past. In such patients, urokinase is an excellent alternative thombolytic agent.

Neutrophil to lymphocyte (N/L) ratio has been associated with in hospital and long term late stent thrombosis [13]. In our study we noticed increased incidence of repeated admission for recurrent PVT

with higher N/L ratio which was statistically significant.

Many studies in the recent few years have shown that the ABO blood groups, particularly the non-O blood groups, are associated with higher risk thrombosis than O blood group (14-17). In our study majority of the patients were having blood group A +ve (40%), and there was no significant difference between O and non- O blood group with respect to successful thrombolysis.

There were many case reports of increased incidence of eosinophilia in patients with recurrent PVT. In our study 11 patients had eosinophilia of >6% there was no significant correlation with response to thrombolysis.

Limitations of the study: The major limitations of the present study are those inherent to retrospective studies. Small sample size of the study population. Trans-oesophageal echocardio-graphy was not done in all patients since TEE is more sensitive test for detection of thrombus. Long term results of thrombolysis are more important which was not studied in the present study.

Future direction:

Trails on fibrin specific thrombolytic agents are required to evaluate the efficacy in PVT. Newer anti coagulants with predictable INR and metabolism are required for management and prevention of PVT.

Conclusion

Recurrent prosthetic valve thrombosis can be treated with thrombolysis with good results. Both urokinase and streptokinase have the same efficacy in recurrent PVT. Neutrophil to lymphocyte ratio was significantly associated with number of trimes patient admitted with recurrent PVT. Patients presenting with NYHA class IV have higher mortality and failure of thrombolysis. Recurrent PVT at mitral position had a higher failure compared to aortic position.

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