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Original Article

ADULT CARDIOLOGY

Effectiveness of Alteplase in Management of Prosthetic Valve Thrombosis in High Risk Surgical Cases

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ABSTRACT

Objective: To determine the effectiveness of alteplase in patients presented with prosthetic valve thrombosis

Study Design: Analytical Cross-Sectional study

Place and Duration of Study: Armed Forces Institute of Cardiology/National Institute of Heart Diseases, Rawalpindi Pakistan from Jan-Sep 2024.

Methodology: Patients aged 18-75years regardless of gender with left-sided mechanical prosthetic valve thrombosis who were deemed high-risk or unfit for surgery were included. Diagnosis was confirmed using transthoracic echocardiography and fluoroscopy. Patients received an accelerated dose of 50mg Alteplase intravenously over 2-hours. Follow-up evaluation included 2D-echocardiography and fluoroscopy 4-hours post-treatment to assess valve function and mobility.

Results: Twenty-two patients [males: 11(50.0%), females:11(50.0%)], with mean age 36.73±14.58years were included in the study. All patients were in NYHA class III-IV and hemodynamically unstable. Fourteen (63.6%) patients experienced Atrial Fibrillation, and 11(50.0%) had suboptimal INR, on admission. Cine-fluoroscopy revealed completely stuck valve in 15(68.2%) patients and mitral valve involved in 17(77.3%) patients. Alteplase showed complete and partial response in 14(63.6%) and 4(18.2%) patients respectively, with overall clinical improvement in 18(81.8%) patients. Patients under 40 years and males showed higher response rate (64.3%) to treatment (p>0.05). Minor bleeding occurred in 3(13.6%) patients, while no major bleeding, stroke, or hematoma was reported.

Conclusion: Alteplase, administered as an accelerated dose of 50mg over 2-hours, is an effective and safe treatment for obstructive prosthetic valve thrombosis in patients at high risk for surgery. With a high rate of clinical improvement and minimal complications, this regimen presents a viable first-line treatment for PVT.

Keywords: Alteplase, Fibrinolytic Therapy, Mechanical Heart Valve, Prosthetic Valve Thrombosis, Thrombolysis

How to Cite This Article: *Ghous MW, Nadeem A, Shah SA, Abbas A, Khan MB, Ateeq M. Effectiveness of Alteplase in Management of Prosthetic Valve Thrombosis, in High Risk Surgical Cases. Pak Armed Forces Med J 2025; 75(Suppl-3): S384-S389. DOI: https://doi.org/10.51253/pafmj.v75iSUPPL-3.12771*

INTRODUCTION

Surgical valve replacement is the standard treatment for valvular heart disease, particularly in patients at low to intermediate surgical risk.[1] mechanical heart valves (MHVs), while durable, are prone to prosthetic valve thrombosis (PVT), a complication that can lead to serious outcomes such as systemic embolism and heart failure due to thrombus formation near the valve.[2] The incidence of PVT varies globally, ranging from 0.1% to 1.3% in developed countries, with higher rates observed in developing nations due to suboptimal anticoagulation therapy.[3]

Treatment approaches for PVT include surgical intervention and fibrinolytic therapy. While surgery remains the definitive treatment, it is associated with significant risks, particularly in patients with comorbidities or those deemed high-risk for surgical intervention.[4] Fibrinolytic therapy using agents like Alteplase, a recombinant tissue plasminogen activator (rt-PA), has gained popularity due to its less invasive nature and ability to rapidly dissolve thrombi, and restoring valve function.[5]

Studies have shown success rates of 70% to 90% for Alteplase, particularly when compared to other thrombolytic agents like streptokinase, which reported a lower efficacy in the PROMETEE study.[6,7] Additionally, Alteplase has demonstrated lower mortality rates at three months compared to surgical intervention in patients with PVT.[8]

However, despite its effectiveness, Alteplase use comes with risks, particularly bleeding complications such as intracerebral hemorrhage.[9] Therefore, careful patient selection and monitoring are crucial. The optimal dosing regimen remains under investigation, with the accelerated Alteplase regimen (50 mg intravenously over two hours) showing promising

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results in patients with NYHA class III and IV heart failure.[10]

Given the limited data on the use of this accelerated Alteplase regimen in local settings, particularly in high-risk surgical patients, this study aims to evaluate its effectiveness as a first-line treatment for obstructive prosthetic valve thrombosis. By addressing this research gap, we hope to provide insights into safer and more effective treatment strategies for high-risk patients, potentially reducing the need for risky surgical interventions.

METHODOLOGY

It was an analytical cross sectional study, conducted over a period of 9 months (Jan 2024 - Sep 2024) at Armed Forces Institute of Cardiology/National Institute of Heart Diseases, Rawalpindi. Sampling Technique used was non-probability consecutive sampling, and study was approved by Institutional Ethical Review Board (Ltr#9/2/R&D/2024/301; Dated: 10th Jan, 2024).

Sample size of 20 was calculated using WHO sample size calculator with confidence level of 95%, margin of error 5%, and using 1.3% prevalence of prosthetic valve thrombosis.[3] However data was collected from 22 patients who fulfilled the study's inclusion criteria.

Inclusion criteria: All patients with age range 18-75 years irrespective of gender, diagnosed to have left sided mechanical prosthetic valve thrombosis, and high-risk or unfit for surgery were included in the study.

Exclusion criteria: Patients with contraindications to fibrinolytic therapy were excluded from the study. These contraindications included a history of previous intracranial hemorrhage, ischemic stroke within the past 3 months, severe uncontrolled hypertension, active internal bleeding, known bleeding disorders, and the presence of a left atrial thrombus on transthoracic echocardiography. Additionally, patients with right-sided prosthetic valve thrombosis were also excluded.(Figure-1)

Patients diagnosed with prosthetic valve thrombosis who met the inclusion criteria were enrolled upon providing written consent. A comprehensive history and physical examination were performed, with symptoms documented, including their duration, heart failure status (classified according to the New York Heart Association (NYHA) class, and the presence of embolic events (peripheral, coronary, or cerebral). Additionally, palpitations and syncope were noted. The diagnosis of PVT was based on elevated transvalvular pressure gradients and impaired leaflet mobility, confirmed by cine fluoroscopy. A mean gradient of ≥10 mmHg for the mitral valve and ≥20 mmHg for the aortic valve was used as the threshold. Details regarding the valve implantation such as; model, size, and position were gathered from the patient's records. Majority of the cases were implanted by Saint Jude Mechanical Valves. ECG was performed to assess rhythm, and INR levels along with all other baseline parameters were recorded upon admission.

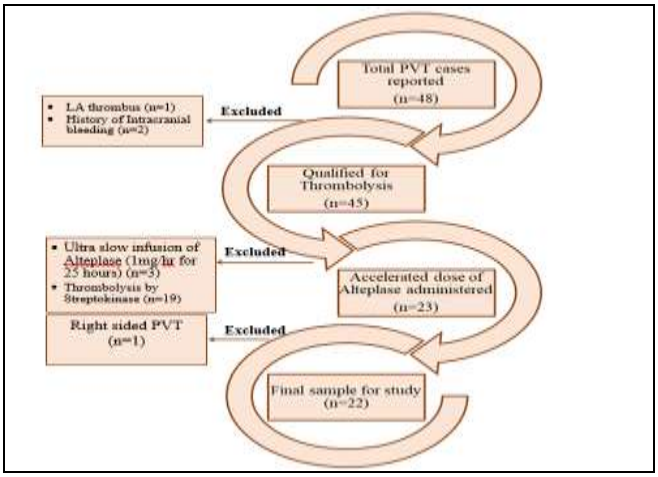

Figure-1: Selection of study participants

A transthoracic echocardiogram (TTE) was performed on all patients. In cases where elevated pressure gradients indicated possible thrombosis, the diagnosis was confirmed via fluoroscopy, which was essential for assessing leaflet mobility, especially in instances of a stuck valve. Upon confirmation, 50 mg of alteplase was administered intravenously over a 2-hour period (accelerated dose). Four hours later, follow-up 2D echocardiography and fluoroscopy were performed to reassess pressure gradients across the valve and evaluate leaflet mobility, determining the effectiveness of the Alteplase treatment.

Statistical analysis was conducted using Statistical Package for Social Sciences (SPSS) version-28:00 Mean and standard deviations were calculated for quantitative variables like age and for categorical variables like gender, onset of symptoms, initial functional class, hemodynamic property, INR on admission, time elapsed after MVR, Cine fluoroscopy and outcome; frequencies/percentages were calculated. Chi-Square test was applied to find association between Alteplase effectiveness and

gender, onset of symptoms, initial functional class, hemodynamic state, INR on admission, time elapsed after MVR, Cine fluoroscopy. *p*-value≤0.05 was taken as statistically significant.

RESULTS

Out of twenty-two patients enrolled in this study, gender distribution was equal, with 11(50.0%) males and 11(50.0%) females and overall mean age of participants was 36.73±14.58 years, so majority had age < 40 years [16(72.7%)]. Symptoms lasted more than 14 days in 11(50.0%) patients and less than 14 days in 11(50.0%). All patients were in NYHA class III-IV 22(100%) and hemodynamically unstable 22(100%). The INR on admission was suboptimal in 11(50.0%) patients. Atrial fibrillation was found in 14(63.6%) patients, majority had MVR within a year 12(54.5%). Cine fluoroscopy revealed 15(68.2%) patients with complete stuck valve. The mean Trans-mitral pressure gradient on ECHO was 26.27±8.59 mmHg. Among complications, 3(13.6%) cases had minor bleeding. The mitral valve was involved in maximum patients 17(77.3%). (Table-I)

Table-II findings revealed that there was no statistically significant association of demographics, clinical parameters and complications with Alteplase effectiveness groups (*p*>0.05). However, the data suggests that patients under the age of 40 showed a higher response rate to Alteplase, with a complete response observed in 9(64.3%) patients. Additionally, gender differences were noted, with males having a more favorable response to Alteplase compared to females (complete response: 64.3% vs. 35.7%). Similarly, maximum patients who showed complete response had >14 days of duration of symptoms 9(64.3%), suboptimal INR 8(57.1%), atrial fibrillation 9(64.3%) completely stuck valve 9(64.3%) and mitral valve was involved in 12(85.7%) patients.

Frequency of Alteplase effectiveness among patients who presented with stuck mitral valve, either partial or complete stuck is illustrated in figure-2.

A complete response to Alteplase was observed in 14(63.6%) patients, a partial response in 4(18.2%) patients, so improved clinical condition was noted in 18(81.8%) patients and a failed response to Alteplase was noted in 4(18.2%) patients.

DISCUSSION

This study demonstrated that Alteplase, administered as an accelerated dose of 50 mg over 2 hours, is an effective treatment for prosthetic valve thrombosis (PVT) in high-risk surgical patients. Complete response was observed in 63.6% of cases, while 18.2% exhibited a partial response, resulting in an overall clinical improvement in 81.8% of the cohort. Notably, there were minimal complications, with only 13.6% of patients experiencing minor bleeding and no cases of major bleeding, stroke, or hematoma were reported.

Table-I: Demographics, Clinical Parameters and Complications of Study Participants (n=22)

Variables	Category	Frequency (%)
Demographics		
Age	< 40 years	16(72.7%)
	≥ 40 years	6(27.3%)
Gender	Male	11(50.0%)
	Female	11(50.0%)
Clinical Parameters		
Duration of Symptoms	>14 days	11(50.0%)
	< 14 days	11(50.0%)
NYHA class	I-II	-
	III-IV	22(100%)
Hemodynamically Stability	Stable	-
	Unstable	22(100%)
INR on Admission	Suboptimal	11(50.0%)
	Optimal	11(50.0%)
Rhythm	Sinus	8(36.4%)
	Atrial Fibrillation	14(63.6%)
Time Elapse After MVR	Within 1 year	12(54.5%)
	More than 1 year	10(45.5%)
Cine Fluoroscopy	Hemi-stuck valve	7(31.8%)
	Stuck valve	15(68.2%)
Valve Involved	Mitral	17(77.3%)
	Aortic	5(22.7%)
Transmitral pressure gradient (mmHg) (Mean±SD)		26.27±8.59
Complications		
Large Subcutaneous Hematoma	Yes	-
	No	22(100%)
Hemorrhagic Stroke	Yes	-
	No	22(100%)
Ischemic Stroke	Yes	-
	No	22(100%)
Bleeding	Yes	3(13.6%)
	No	19(86.4%)

**NYHA= New York Heart Association Classification; INR=International Heart Association; MVR= mitral valve replacement ECHO=Echocardiography; MVR=Mitral Valve Regurgitation*

Multiple research studies have demonstrated the efficacy of Alteplase in treating a life-threatening complication, the PVT, making it a feasible therapy

Table II: Association of Alteplase effectiveness with demographics, clinical parameters and complications (n=22)

Variables Frequency (%)		Alteplase Effectiveness			*p*-value
		Complete Response (Total=14)	Partial Response (Total=4)	Failed Response (Total=4)	
Demographics					
Age	< 40 years	9(64.3%)	4(100%)	3(75.0%)	0.55
	≥40 years	5(35.7%)	0(0.0%)	1(25.0%)	
Gender	Male	9(64.3%)	1(25.0%)	1(25.0%)	0.26
	Female	5(35.7%)	3(75.0%)	3(75.0%)	
Clinical Parameters					
Onset of Symptoms	> 14 days	9(64.3%)	0(0.0%)	2(50.0%)	0.17
	< 14 days	5(35.7%)	4(100%)	2(50.0%)	
INR on Admission	Optimal	6(42.9%)	1(25.0%)	4(100%)	0.17
	Suboptimal	8(57.1%)	3(75.0%)	0(0.0%)	
Rhythm	Sinus	5(35.7%)	2(50.0%)	1(25.0%)	1.00
	Atrial Fibrillation	9(64.3%)	2(50.0%)	3(75.0%)	
Time Elapse After MVR	Within 1 year	7(50.0%)	3(75.0%)	2(50.0%)	0.83
	More than 1 year	7(50.0%)	1(25.0%)	2(50.0%)	
Cine Fluoroscopy	Hemi-stuck valve	5(35.7%)	0(0.0%)	2(50.0%)	0.45
	Stuck valve	9(64.3%)	4(100%)	2(50.0%)	
Valve Involved	Mitral	12(85.7%)	3(75.0%)	2(50.0%)	0.48
	Aortic	2(14.3%)	1(25.0%)	2(50.0%)	
Complications					
Bleeding	Yes	2(14.3%)	0(0.0%)	1(25.0%)	1.00
	No	12(85.7%)	4(100%)	3(75.0%)	

INR=International Heart Association; MVR= Mitral Valve Replacement

option for patients who are not immediately able to undergo surgery or who are at high risk for surgical intervention.[11,12] The effectiveness of Alteplase in managing PVT demonstrates consistent outcomes, as evident from 81.8 % clinical improvement in current study. These results aligned with existing literature, though variations in response rates (70-90% success rate) across studies highlighted the complexity of treating PVT.[6,7]

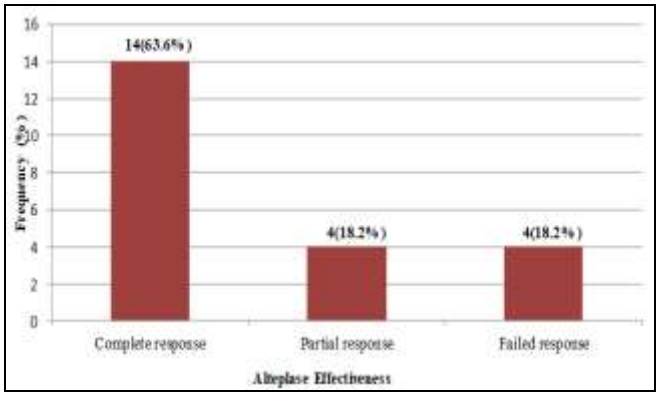

Figure-2: Alteplase Effectiveness In Patients with Stuck Mitral Valve (n=22)

The PROMETEE trial, conducted in Europe, validated Alteplase as a first-line treatment for obstructive PVT, reported an impressive success rate of approximately 90%.[7] While our study's response rate (63.6%) was lower, it remains significantly higher than the 47.05% complete response rate observed in the 2018 study.[13] at AFIC, where streptokinase was employed as the thrombolytic agent . The reduced side effect profile observed with Alteplase in our study, including the absence of significant bleeding or non-CNS embolic events, suggested that Alteplase may offer a safer alternative to streptokinase for PVT management. These findings reinforce Alteplase's growing preference in clinical practice, especially in high-risk surgical population.

A meta-analysis comparing thrombolytic therapy to surgical intervention for PVT demonstrated that thrombolysis is associated with significantly lower mortality rates than surgery.[14] This supports our decision to use Alteplase as the treatment of choice in patients at high surgical risk. Similarly, an Indian study comparing surgical valve replacement with thrombolytic therapy found that while surgery remains effective, it poses higher risks, especially in critically ill patients. Thrombolytic therapy, particularly with Alteplase, had shown favorable outcomes in such populations, although the risk of complications, such as bleeding and embolism, persists.[15]

Interestingly, a study in the European Heart Journal-Cardiovascular Pharmacotherapy highlighted

the influence of infusion protocols on the efficacy of Alteplase in PVT treatment. It demonstrated that an ultra-slow Alteplase infusion regimen (1 mg/hour for 25 hours) achieved complete thrombolysis in 85.0% of patients, compared to 78.3% in a fast-protocol group (25 mg over 6 hours).[16] Although we employed an accelerated regimen of 50 mg over 2 hours in our study, the substantial clinical improvement and minimal complications suggest that Alteplase is effective across various protocols, though slower regimens may offer enhanced safety and efficacy in some cases. This is consistent with emerging literature advocating for slower Alteplase infusions as a first-line therapy due to their favorable clinical outcomes and reduced complication rates, particularly when compared to surgical options.[17]

The frequency of PVT in developing countries, including those seen in our cohort, can often be attributed to inadequate anticoagulation management, with sub-therapeutic levels of the International Normalized Ratio (INR) being a major contributor.[18] In our study, 50% of patients presented with suboptimal INR levels, emphasized the importance of stringent anticoagulation monitoring to reduce PVT occurrence. Alteplase's mechanism of action, which involves converting plasminogen to plasmin and subsequently breaking down fibrin clots, remains a potent strategy for resolving obstructive PVT.[19]

Thereby, the Alteplase administration as an accelerated dose of 50 mg over 2 hours, has proven to be a highly effective and safe treatment for PVT in high-risk surgical patients. Compared to older agents like streptokinase and surgical intervention, Al teplase offers a more favorable risk-benefit profile, with fewer complications and better clinical outcomes. Further research, particularly comparing different Alteplase infusion regimens, will help optimize treatment protocols and improve patient care in both developed and developing countries.

LIMITATIONS OF STUDY

This study has two key limitations. First, the study evaluated the response to a single dose of Alteplase, without exploring the potential benefits of repeated dosing. Secondly, it was a single-centered study, which may limit the generalizability of the findings to broader populations, as treatment protocols and patient characteristics can vary across institutions.

CONCLUSION

This study demonstrated that alteplase, administered as an accelerated dose of 50 mg over 2 hours, is an effective treatment option for PVT, particularly in patients who are high-risk surgical candidates. With a complete response rate of 63.6% and an overall clinical improvement observed in 81.8% of patients, alteplase presents a viable alternative to surgery, with fewer complications than previously reported with other thrombolytic agents like streptokinase.

ACKNOWLEDGEMENT

We are highly obliged to our consultants for their guidance, support and patience that greatly assisted our research. we would also like to pay our gratitude to Exec Dir Comdt AFIC and R&D department for their support and contribution to complete this research paper.

Conflict of Interest: None

Authors' Contribution

Following authors have made substantial contributions to the manuscript:

MWG & AN: Study concept, study design, drafting the manuscript, approval of the final version to be published

SAS & AA: Study concept, data acquisition, critical review, approval of the final version to be published

MBK & MA: Data acquisition, data analysis, data interpretation, approval of the final version to be published

Authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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