

## Fibrinolytic Therapy in Thrombosis of Mechanical Valves: Outcomes and Complications

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### Original Article

#### Abstract

**INTRODUCTION:** Valvular heart disease presents a significant and escalating global health challenge. Prosthetic valve thrombosis (PVT) following surgical valve replacement is a primary cause of valve failure. The aim of this study was to ascertain the outcomes and complications of fibrinolytic therapy in patients diagnosed with PVT.

**METHOD:** This cross-sectional study enrolled 81 patients diagnosed with PVT who underwent fibrinolytic therapy between 2008 and 2018. Streptokinase was administered to 87.6% of patients, while 12.4% received reteplase. All demographic and clinical data were gathered from the patients' medical records. The incidence of successful recovery and complications were assessed.

**RESULTS:** The records of 81 patients (43.2% male, mean age:  $51.6 \pm 13.9$  years) were examined. The findings revealed that 59% and 35% of the patients had mitral and aortic PVT, respectively. While 12% of the patients experienced drug complications, 90% achieved successful recovery. Stroke and severe hemorrhage were complications frequently reported by the patients treated with streptokinase (8% and 4% respectively). The patients treated with reteplase demonstrated a 100% recovery rate. Conversely, 89% of the patients treated with streptokinase achieved successful recovery, and 7% of the patients experienced a partial recovery.

**CONCLUSION:** Fibrinolytic agents can serve as an effective treatment with an excellent success rate for managing PVT in patients post-surgical valve replacement.

**Keywords:** Prosthetic valve thrombosis, Fibrinolytic therapy, Streptokinase, Reteplase

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#### Introduction

Valvular Heart Disease (VHD) is among the most prevalent cardiovascular diseases, impacting over 2.5 percent of the global population and significantly influencing the mortality, morbidity, and burden of cardiovascular diseases worldwide <sup>1,2</sup>. It is clinically characterized as a structural or functional abnormality of a cardiac valve that disrupts the unidirectional blood flow during

the cardiac cycle <sup>2</sup>. VHD can be attributed to various etiologies, including rheumatic, degenerative, traumatic, congenital, and infectious heart diseases <sup>3</sup>. The epidemiology of VHD varies significantly across the globe, with degenerative diseases predominating in industrialized countries and rheumatic heart disease being more common in developing and low-income countries <sup>4</sup>. However, recent studies indicate an increasing burden of non-rheumatic valvular heart diseases in developing

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countries as well <sup>5</sup>.

Valvular surgeries have been prevalent over the past decade, accounting for more than 20% of all cardiac operations <sup>6</sup>. At present, surgical valve replacement is recognized as a standard therapeutic approach for VHD in patients with low and intermediate risk of surgery <sup>7</sup>. Mechanical and bioprosthetic valves are the two commonly used types of surgical prosthetic heart valves. While new-generation prosthetic valves are less thrombogenic, mechanical heart valves are more susceptible to thrombosis due to their physical and hemodynamic properties <sup>8</sup>. Prosthetic Valve Thrombosis (PVT) is one of the major causes of primary valve failure. In mechanical valves, the incidence rate of PVT ranges from 0.5 to 8% in mitral and aortic valves and up to 20% in tricuspid valves <sup>9,10</sup>. Overall, an annual episode of PVT has been reported in up to 5.7% of patients with mechanical heart valves <sup>11</sup>.

Surgery, heparin anticoagulation therapy, and thrombolytic therapy are among the therapeutic modalities for PVT. These are influenced by the patient's clinical status, valve location, and the extent of valvular obstruction <sup>12-14</sup>. Intravenous thrombolysis offers a non-invasive alternative to surgical interventions. Studies suggest that for patients with PVT, thrombolysis is an appealing first-line treatment, yielding clinical results comparable to surgical methods <sup>15,16</sup>. However, different outcomes and varying degrees of safety have been reported following the initiation of treatment with common thrombolytic agents <sup>17</sup>. Due to various conditions, including a scarcity of surgical skill, the high cost of surgery, and patient preference for non-surgical options, thrombolytic therapy is becoming the first-line treatment in most developing countries, with streptokinase being a widely used drug <sup>18</sup>. Therefore, to further elucidate the efficacy of thrombolysis, this study aimed to determine the outcomes and complications of fibrinolytic therapy in patients with PVT.

## Materials and Methods

In this cross-sectional study, the records

of 81 patients diagnosed with PVT who were hospitalized between 2008 and 2018 in Chamran Hospital, Isfahan, Iran, were assessed. Patients with prosthetic mechanical heart valves and confirmed PVT were eligible if they had received fibrinolytic therapy and had no history of previous intracranial hemorrhage or ischemic stroke within the last 3 months, and no history of intracranial or spinal cord surgery. The protocol of this study was reviewed and approved by the Ethics Committee of Isfahan University of Medical Sciences.

Demographic characteristics and clinical data, including the time elapsed since valve replacement, type of valve (monoleaflet/bileaflet), valve location (mitral/aortic/tricuspid/pulmonary), clinical signs and symptoms at admission, drug complications, the international normalized ratio (INR), the length of hospital stay, treatment outcomes (successful recovery, partial recovery, and death), and survival at the time of hospitalization were obtained from the patients' medical records. Successful recovery was defined as the reversal of the echocardiographic gradient of valves to the normal baseline and return to normal leaflet motion in fluoroscopy. Partial recovery was defined as either an intermediate reduction in the transvalvular gradients from the baseline or restricted movement of prosthetic valve leaflet(s) on fluoroscopy, even if the transvalvular gradients completely normalized.

## Statistical Analysis

Data analysis was performed using SPSS (version 24) for Windows (SPSS Inc., Chicago, IL, USA). The descriptive statistics were presented as means  $\pm$  SD for continuous variables and as numbers (percent) for categorical variables. The independent sample t-test and chi-square test were used to compare the continuous and categorical data between the patients treated with streptokinase or reteplase, respectively. Statistical significance was set at P-values less than 0.05 ( $<0.05$ ).

## Results

The data of 81 patients who were diagnosed

with PVT between 2008 and 2018 and were treated with fibrinolytic agents were analyzed. Table 1 shows the demographic and clinical characteristics of the patients. The mean ( $\pm$ SD) age of the patients was 51.6 ( $\pm$ 13.9) years. Among the patients, 43% were male and 57% were female. The type of mechanical valves was bileaflet in 94% of the patients and monoleaflet in 6%. In most of the studied

patients, the mechanical valve position was in the mitral (58%) and aortic (35%) area. Cardiac dyspnea (84%) and chest pain (31%) were the most frequent symptoms of the patients. Nearly 12% of the patients had drug complications. Most of the patients had successful recovery (90%) and three patients died. Survival at the time of hospitalization was 96%.

**Table 1.** Demographic and clinical characteristics of studied patients

	All studied patients	SK (n = 71)	r-PA (n = 10)	p-value
<b>Age (year)</b>	51.6 $\pm$ 13.9 [22-86]	51.4 $\pm$ 14.3	52.8 $\pm$ 11.7	0.766 *
<b>Gender</b>				
Male	35 (43)	30 (42.2)	5 (50)	0.643 †
Female	46 (57)	41 (57.8)	5 (50)	
<b>Time from valve replacement (year)</b>	8.3 $\pm$ 6.0	8.1 $\pm$ 6.3	9.8 $\pm$ 3.8	0.409 *
<b>Valve type</b>				
Monoleaflet	5 (6)	5 (7)	0 (0)	0.508 **
Bileaflet	76 (94)	66 (93)	10 (100)	
<b>Valve location replacement</b>				
Mitral	47 (59)	40 (57.1)	7 (70)	0.866 **
Aortic	28 (35)	25 (35.7)	3 (30)	
Tricuspid	4 (5)	4 (5.7)	0 (0)	
Pulmonary	1 (1)	1 (1.4)	0 (0)	
<b>Clinical signs and symptoms at admission</b>				
Valve noise reduction	17 (21)	17 (23.9)	0 (0)	
Cardiac dyspnea	68 (84)	60 (84.5)	8 (80)	0.081**
Chest pain	25 (30.9)	20 (28.2)	5 (50)	
Edema	18 (22.2)	17 (23.9)	1 (10)	
Arrhythmia	10 (12.2)	7 (9.9)	3 (30)	
Cardiogenic shock	1 (1.2)	1 (1.4)	0 (0)	
<b>Drug complication</b>				
Severe Hemorrhage	3 (3.7)	3 (4.2)	0 (0)	0.181**
Thromboembolism	1 (1.2)	1 (1.4)	0 (0)	
Stroke	6 (7.4)	6 (8.4)	0 (0)	
<b>INR</b>	2.15 $\pm$ 1.20	2.07 $\pm$ 1.12	2.69 $\pm$ 1.64	0.128 *
<b>Hospital LOS</b>	10.7 $\pm$ 7.1 [1-53]	10.6 $\pm$ 7.3	11.4 $\pm$ 4.9	0.737 *
<b>Outcome</b>				
Successful recovery	73 (90.1)	63 (88.7)	10 (100)	0.670**
Partial recovery	5 (6.2)	5 (7)	0 (0)	
Death	3 (3.7)	3 (4.2)	0 (0)	

The data are presented as Mean  $\pm$  SD [Min-Max], Mean  $\pm$  SD, Number, and Number (%).

P-values calculated by \*Independent sample t-test, † chi-square test, and \*\*Fisher exact test.

SK, streptokinase; r-PA, reteplase; M, Male; F, Female; LOS, the length of stay; INR, the International normalized ratio. LOS, Length of stay; INR, International normalized ratio.

Among the patients studied, 71 patients (87.6%) were treated with streptokinase and 10 patients (12.4%) were treated with reteplase. Age, gender, time elapsed since valve replacement, and signs and symptoms showed no significant differences between the patients treated with streptokinase or reteplase (Table 1). All patients who experienced drug complications had been treated with streptokinase. Furthermore, stroke and severe hemorrhage were reported as the two most frequent complications, with an incidence rate of 8% and 4%, respectively. Successful recovery in the patients treated with reteplase was 100%. Among the patients treated with streptokinase, three patients died, five patients had partial recovery, and 89% had a successful recovery. Due to the reluctance of surgeons to perform prosthetic valve thrombosis surgery, only one case of thrombotic mitral valve surgery was performed during this period, which was quite successful. In this study, three pregnant women with prosthetic mitral valve thrombosis were treated with streptokinase and had successful recovery. However, abortion occurred in one case two hours after streptokinase injection.

### Discussion

PVT is one of the major causes of primary valve failure, and fibrinolytic therapy is the main treatment option in patients with PVT in developing countries. This study assessed the outcomes and complications of fibrinolytic therapy in patients with PVT. The results showed that only 15% of the patients had drug complications. Stroke (8%) and severe hemorrhage (4%) were the two most frequently reported complications. It was also shown that 96% of the patients had (successful or partial) recovery, and only three patients did not respond to treatment and died. The outcomes and complications in the patients treated with reteplase were better than those treated with streptokinase. Overall, good outcomes and the low incidence of adverse events in both fibrinolytic agents showed that fibrinolytic therapy can be considered as an efficient treatment in patients with PVT.

Although controversies exist on the comparison of surgery and thrombolytic therapy in the management of PVT, many studies have underscored the positive outcomes of thrombolytic therapies in treating PVT. Özkan et al. have recently demonstrated that thrombolytic therapy resulted in a success rate of almost 90%. The authors reported that low-dose and slow/ultraslow t-PA infusions have been associated with low complications and mortality, as well as high success rates, and should be regarded as a feasible therapy option in patients with PVT<sup>19</sup>. Previously, Keuleers et al. had demonstrated that the clinical outcomes of thrombolysis as first-line therapy in PVT were favorably comparable to surgical approaches<sup>15</sup>.

The current study showed that nearly 96% of the patients treated with streptokinase had recovery (89% had successful recovery and 7% partial recovery). In line with the authors' findings, Sharma et al. reported that of 48 patients treated with streptokinase, 90% had a recovery, (81% successful recovery and 8% partial recovery)<sup>20</sup>. Additionally, Pradhan and colleagues also reported a success rate of 81% in treating PVT patients using streptokinase<sup>21</sup>, while Abbas et al. demonstrated a successful treatment using streptokinase in nearly 74% of PVT cases<sup>18</sup>. In a recent study by Manandhar et al., 83% of the PVT patients receiving streptokinase showed successful recovery<sup>22</sup>.

The findings of the current study also highlighted the beneficial role of reteplase in treating PVT. All patients treated with reteplase had a successful recovery. However, studies on third-generation recombinant tPA, such as reteplase, in the management of PVT are limited. In a case report by Bagheri et al., successful treatment of prosthetic pulmonary valve thrombosis with reteplase was reported<sup>23</sup>. In another study, Behzadnia and colleagues reported four cases of recurrent prosthetic valve thrombosis that were successfully treated with reteplase<sup>24</sup>.

Regarding the complications of fibrinolytic therapy, Karthikeyan et al. reported the incidence of complications including death, major bleeding, embolic stroke, or non-

central nervous system systemic embolic event in 16.7% of the patients with PVT after fibrinolytic therapy using streptokinase <sup>25</sup>. Abbas et al. reported minor bleeding (4.8%) and major bleeding (12%) as the most common complications after receiving streptokinase in PVT patients <sup>18</sup>. Similarly, the current study reported complications in 14.1% of the patients treated with streptokinase. However, 4% of these patients died during their hospital stay.

The current study had several limitations. First, because of the historical design of the study, the authors were not able to determine the time of treatment-related adverse events concerning the duration of fibrinolytic therapy. Second, the small number of patients treated with reteplase could have limited the statistical power of the study to detect a significant association. Thus, further studies with a prospective design and larger sample size are required to clarify the outcomes and complications of fibrinolytic therapy in patients with PVT.

In conclusion, the authors' results showed a successful recovery rate of 90% with a low incidence of adverse events after fibrinolytic therapy in the patients with PVT. The successful and partial recovery rates of thrombolytic therapy with reteplase and streptokinase in PVT were similar, so fibrinolytic agents can be considered as an effective therapy with an excellent success rate for the management of PVT in patients after surgical valve replacement.

### **Ethics approval and consent to participate**

The study was approved by the ethics committee of Isfahan University of Medical Sciences with ID number IR.MUI.REC.1396.684. Ethical considerations were taken into account during data collection and analysis. Written informed consent was obtained from the participants before starting data collection. It was assured that confidentiality would be maintained and that no personal information would be mentioned in the publications arising from the study. The participants were informed that participation was entirely voluntary and they could withdraw at any time.

### **Consent for publication**

Not applicable.

### **Availability of data and materials**

The datasets generated during the current study can be provided by the corresponding author upon reasonable request.

### **Competing interests**

The authors declare that they have no competing interests.

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### **Authors' contributions**

ANN and FY performed data extraction, conducted data analysis, and prepared the original manuscript, as well as wrote the first draft of the manuscript. MA extracted data. ANN, FY, RZ, and AA contributed to consultations and data collection, and supervised the project. They also monitored the implementation of the study and were involved in the preparation of the manuscript. All authors read and approved the final manuscript.

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