International Journal of Research in Medical Sciences
Purushotama TS et al. Int J Res Med Sci. 2020 Feb;8(2):575-579
www.msjonline.org
pISSN 2320-6071 | eISSN 2320-6012
DOI: http://dx.doi.org/10.18203/2320-6012.ijrms20200238

Original Research Article

Efficacy and safety of thrombolytic therapy in prosthetic valve thrombosis

Purushotama T. S.[1]*, Sathish K.[2], Santhosh K.[1], Ravindranath K. S.[2], Manjunath C. N.[2]

[1]Department of Cardiology, Sri Jayadeva Institute of Cardiovascular Science Research (SJICSR) Centre, Mysore, Karnataka, India
[2]Department of Cardiology, Sri Jayadeva Institute of Cardiovascular Science Research Centre, Bangalore, Karnataka, India

Received: 02 December 2019
Revised: 26 December 2019
Accepted: 31 December 2019

***Correspondence:**
Dr. Purushotama T. S.,
E-mail: purushts@gmail.com

ABSTRACT

Background: There is limited data available about the effectiveness of thrombolysis in prosthetic valve thrombosis (PVT). Therefore, this study aimed to evaluate the efficacy and safety of thrombolytic treatment in PVT patients.
Methods: This was an observational study conducted at a tertiary-care centre in India between March 2013 and April 2014. Total of 56 patients with either recurrent PVT or with confirmed left-sided PVT was included in the study. Thrombolytic therapy was administered as an intravenous infusion of streptokinase or urokinase, initially at a loading dose of 2.5L IU/hour over 30 minutes, followed by 1L IU/hour for 48–78 hours depending upon the clinical and 2D-Echo observation. Primary endpoint was considered as the occurrence of a complete clinical response. Secondary endpoint was considered as a composite of death, major bleeding or embolic stroke.
Results: Mean age of the patients was 37±13 years. Most of the patients presented with NYHA-II (51.7%), III (39.2%), and IV (8.9%) symptoms. Mitral and aortic valve thrombosis were observed in 40(71.4%) and 11(28.6%) patients. Forty-nine (73.3%) patients were treated with streptokinase. Whereas, rethrombosis patients were treated with urokinase [6(16%)] and tenecteplase [1(1.3%)]. Two (3.6%) patients died, 1(1.8%), 1(1.8%), 2(3.6%), and 1(1.8%) patient had peripheral embolism, central nervous system bleeding, stroke, and embolic complications.
Conclusions: Thrombolytic therapy can be used as the first-line treatment for thrombolysis in PVT patients. All PVT patients can be treated with streptokinase unless specific contraindications exist. Urokinase or tenecteplase is an alternative thrombolytic agent in rethrombosis patients.

Keywords: Prosthetic valve thrombosis, Streptokinase, Thrombosis, Thrombolytic treatment

INTRODUCTION

Valve replacement surgery for multivalvular disease such as rheumatic heart disease is more common in India and these patients will have high early and late prosthetic valve malfunction because of primary valve failure, valve thrombosis, endocarditis, thromboembolism, and hemolytic anemia.[1,2] Prosthetic valve thrombosis (PVT) is one of the major causes of primary valve failure and has an incidence from 0.1% to 6% per patient per year of aortic and mitral valves, and up to 20% of tricuspid valves.[1-3] The incidence of PVT depends on valve type and position, anticoagulation status, presence of atrial fibrillation and/or ventricular dysfunction.[4] Among these, the most common cause is inadequate anticoagulant therapy because even with the use of warfarin therapy the incidence of thromboembolism is 1-2% per year, but the risk is considerably higher without treatment with warfarin.[1,2,5]

Recent studies have shown that thromboembolism is greater in the mitral prosthetic valve position (mechanical or biological) than with one in the aortic position.[1,2] Early diagnosis and suitable treatment should be quickly established because diagnostic tools such as cinefluoroscopy, transthoracic and transesophageal echocardiography have been challenging mainly due to variable clinical presentations and the degree of valvular obstruction.[6,7] Emergency surgery (valve replacement) has been the traditional treatment but the presence of valvular obstruction or the site of the thrombotic valve (left or right-sided) changes the treatment approach. Fibrinolytic therapy has been proposed as an alternative to surgery and is considered to be the treatment option for this complication.[8] This thrombolytic therapy will not preclude surgical treatment in the event of treatment failure.[9] Recently, urokinase and tenecteplase have been shown success and effectiveness in recurrent PVT or in streptokinase treatment failure patients.[10] There is limited data available about the effectiveness of thrombolytic treatment in PVT. Therefore, this study was conducted to evaluate the efficacy and safety of thrombolytic treatment in PVT patients.

METHODS

This was an observational study conducted at a tertiary-care center in India between March 2013 and April 2014. A total of 56 patients with either recurrent PVT or with confirmed left-sided PVT were included in the study. Patients with contraindications to thrombolytic therapy including any previous intracranial hemorrhage, ischemic stroke within the last 3-months, presence of a left atrial thrombus on transthoracic echocardiography, and pregnancy were excluded in the study. Signed informed consent was obtained from all the patients.

Thrombolytic regime

Thrombolytic therapy was administered as an intravenous infusion of streptokinase or urokinase, initially at a loading dose of 2,50,000 IU/hour over 30 minutes, followed by 1,00,000 IU/hour for 48-78 hours depending upon the clinical and 2D-Echo observation. In some patients, tenecteplase was administered at an average dose of 1.01 mg/kg (0.63-1.2 mg/kg). Doppler transthoracic echocardiography was performed to observe the abnormal trans-prosthetic flow or central regurgitation indicating abnormal valve closure. Once ended the streptokinase therapy, unfractionated heparin was started as a continuous intravenous infusion of 5000 IU 6 hourly and overlapped with other anticoagulants. Heparin was continued until the target international normalized ratio (INR) was achieved with an oral anticoagulant. Patients were monitored for adverse events until they were discharged from the hospital. At the time of discharge, successfully thrombolysis patients were prescribed with 75-150 mg of aspirin apart from anticoagulants such as warfarin or nicoumalone to maintain INR between 2 and 2.5.

Definitions and endpoints

The primary endpoint was considered as the occurrence of a complete clinical response (defined as a complete restoration of valve function in the absence of death, major bleeding or embolic stroke). The secondary endpoint was considered as a composite of death, major bleeding or embolic stroke. Completed restoration of valve function consisted of restoration of normal leaflet motion and normalization of transvalvular pressure gradients such as the mitral mean diastolic gradient of 6 mmHg, the end-diastolic gradient of 2 mmHg, and aortic peak gradient of 30 mmHg on Doppler echocardiography.

Fibrinolytic therapy was considered as failed when transvalvular gradients were not reduced by <50% from baseline, with persistent leaflet abnormality, or if a complication resulted in death irrespective of whether valve function was restored. Partial response is defined as improvement in transvalvular gradients <50% from baseline but without complete normalization of leaflet motion. Major bleeding is defined as intracranial bleeding, required transfusion, or led to surgical exploration. Other bleeding episodes were considered as minor. Embolic stroke is defined as any focal neurological deficit that lasted 24 hours with brain imaging suggestive of a primary ischemic origin. All patients with a suspected ischemic stroke or intracranial hemorrhage underwent brain imaging.

Statistical analysis

Continuous variables were presented as mean ± standard deviation and categorical variables as counts and percentages. All statistical analysis was performed by using statistical package for social sciences (SPSS) software (SPSS Inc.; 17.0 version, Chicago, Illinois, USA).

RESULTS

A total of 56 patients with a mean age of 37±13 years were identified and analyzed in the study. The female predominance was observed in the study population. At the time of admission, the clinical presentation was a gradual onset of breathlessness or acute pulmonary edema. Besides, 29(51.8%), 22(39.3%), and 5(8.9%) patients had NYHA-II, III, and IV status of dyspnea, respectively. Mitral valve thrombosis and aortic valve thrombosis was observed in 40(71.4%) and 11(19.6%) patients, respectively. Whereas, double valve thrombosis was observed in 5(8.9%) patients.

Among 56 patients, 54(96.5%) patients had mechanical prosthetic valve thrombosis and two (3.6%) patients had bioprosthetic valve thrombosis. Of the 54 patients, 27(48.1%), 17(30.4%), 9(16.1%), and 1(1.8%) patients had St. Judes, Medtronic ATS, TTK Chitra, and Start Edward mechanical prosthetic valve thrombosis.

Table 1: Baseline clinical characteristics of the study population.

Variables		Patients (N=56)
Age (Mean±SD, years)		37±13
Female, n (%)		29 (51.8%)
Duration of symptom onset and treatment, days		3-4
NYHA Class	Class II, n (%)	29 (51.8%)
	Class III, n (%)	22 (39.3%)
	Class IV, n (%)	5 (8.9%)
Site of the prosthetic valve	Mitral valve, n (%)	40 (71.5%)
	Aortic valve, n (%)	11 (19.6%)
	Double valve, n (%)	5 (8.9%)
Prosthetic valve type	St. Judes, n (%)	27 (48.1%)
	Medtronic ATS, n (%)	17 (30.4%)
	TTK Chitra, n (%)	9 (16.1%)
	Star Edward, n (%)	1 (1.8%)
	Bioprosthetic, n (%)	2 (3.6%)
Thrombolytic agent	Streptokinase, n (%)	49 (87.5%)
	Urokinase, n (%)	6 (10.7%)
	Tenectaplase, n (%)	1 (1.8%)
	INR range, Mean (range)	2.16 (1.12-3.2)

NYHA–New York Heart Association; INR–International normalized ratio

All patients were having rheumatic heart disease and a higher number of patients were treated with streptokinase 49(87.5%). Whereas, rethrombosis patients were treated with urokinase [6(10.7%) patients] and tenecteplase [1(1.8%) patient]. All patients in the study population received an oral anticoagulant either in the form of warfarin or nicoumalone for prevention of valve thrombosis and their INR at the time of valve thrombosis ranged from 1.12-3.2. Baseline clinical characteristics of the study population are displayed in Table 1.

As shown in Table 2, seven patients had complications after thrombolytic therapy in the study population. Of which, two patients died, 1(1.8%), 1(1.8%), 2(3.6%), and 1(1.8%) patient had peripheral embolism, central nervous system bleeding, stroke, and embolic complications, respectively. The average mean transvalvular pressure valve gradient (TVG) in the mitral valve thrombosis was noted with more than 50% reduction from 19.3±7.4 mmHg before thrombolysis to 8.9±2.6 mmHg after thrombolysis. Also, more than 50% reduction of average mean TVG in the aortic valve was observed from 55.1±17.3 mmHg before thrombolysis to 13.6±3.3 mmHg after thrombolysis. The remaining comparison of the transvalvular pressure gradient between pre- and post-thrombolysis in the study population is depicted in Table 3.

Table 2: Complications after thrombolytic therapy in the study population.

Complications	Patients (N=56)
Peripheral embolism, n(%)	1 (1.8%)
Central nervous system bleeding, n(%)	1 (1.8%)
Stroke, n(%)	2 (3.6%)
Bleeding with transfusion, n(%)	0 (0%)
Death, n(%)	2 (3.6%)
Embolic complications, n(%)	1 (1.8%)

Table 3: Comparison of transvalvular pressure gradient between pre- and post-thrombolysis in the study population.

Outcomes	Pre-thrombolysis (N=56)	Post- thrombolysis (N=56)
Mitral valve replacement		
Average peak TVG (Mean±SD, mmHg)	31.7±9.6	14.5±4.3
Average mean TVG (Mean±SD, mmHg)	19.3±7.4	8.9±2.6
Aortic valve replacement		
Average peak TVG (Mean±SD, mmHg)	90.7±25.5	24±5.8
Average mean TVG (Mean±SD, mmHg)	55.1±17.3	13.6±3.3

TVG–Transvalvular pressure gradient.

DISCUSSION

The traditional treatment for the management of PVT has been thrombectomy or valve replacement, but it incurs a major limitation of high surgical mortality.[11] The high mortality rates have led to an increased usage of thrombolysis which has been easy to administer, cost-effective, and associated with lower mortality rates than surgery. In the current study, all patients with PVT were managed with thrombolysis using either streptokinase, urokinase or tenecteplase.

In this study, PVT was more common in women (51.8%) which is similar to the previous studies conducted in India showing that women have been more susceptible to PVT.[12] The results of this study support the findings of

studies by Patil S, et al. and Gupta, et al. showing that mitral valve prosthesis was most commonly involved in the majority of the patients (71.5%) compared to aortic valve prosthesis (19.6%).[13,14] Parallelly many studies have confirmed that occurrences of mitral PVT have been 2–3 times greater than with aortic PVT.[6,15] Besides, the majority of the patients in this study population have mechanical valve involvement than bioprosthetic valves and also higher number of patients had NYHA class II symptoms followed by III and IV symptoms which were similar to a study conducted by Patil S, et al.[13] Streptokinase (87.5%) was the most commonly administered agent for thrombolysis followed by urokinase (10.7%) and tenecteplase (1.8%).

Thrombolysis has been successful in 87.5% of the patients with a mortality rate of 3.6%. Similarly, several studies suggest that the success rate with fibrinolytic therapy is at least 80%.[16-18] Streptokinase is widely available in most of the tertiary-care centers in India and is cost-effective. However, in recurrent PVT patients, urokinase or tenecteplase is an excellent alternative thrombolytic agent.

In thrombolysed patients, embolism and stroke were observed in 1.8% and 3.6% of study population which was lower than other studies showing that 12% to 17% of patients have occurred with embolic risk caused by thrombolysis.[19,20] Whereas, embolic complications depend on the obstruction but not on the thrombus size.[21,22] Hence, heparin treatment might be a successful treatment option for patients with non-obstructive PVT. Moreover, according to our knowledge, this is the first study to compare the transvalvular pressure gradient before and after thrombolysis. It was observed that thrombolytic therapy improved the pressure gradient after thrombolysis. This evidence favors non-invasive thrombolytic therapy as a first-line treatment option irrespective of obstruction and functional class in the absence of contraindication. Heparin can be used initially for small non-obstructive thrombi only if thrombolysis is contraindicated.

Overall, thrombolytic therapy efficacy in PVT is high with a low complication and mortality rate. Furthermore, thrombolysis guided by transthoracic echocardiography is a safe and effective method that may expand the indications for nonsurgical treatment of PVT. By using serial echocardiography, the dose and duration of thrombolytic therapy can be tailored to the patient's requirement for normalization of valve hemodynamics.

CONCLUSION

Thrombolytic therapy can be used as the first-line treatment for thrombolysis in PVT patients. Thrombolytic treatment for PVT may improve clinical outcomes by improving hemodynamic conditions with lower risk. Streptokinase is an efficacious and safe thrombolytic drug in the treatment of PVT. All PVT patients can be treated with streptokinase unless specific contraindications exist. Urokinase or tenecteplase is an alternative thrombolytic agent in rethrombosis where streptokinase cannot be used.

Funding: No funding sources
Conflict of interest: None declared
Ethical approval: The study was approved by the Institutional Ethics Committee

REFERENCES

1. Grunkemeier GL, Li HH, Naftel DC, Starr A, Rahimtoola SH. Long-term performance of heart valve prostheses. Curr Probl Cardiol. 2000;25(2):78-147.
2. Cannegieter S, Rosendaal F, Briet E. Thromboembolic and bleeding complications in patients with mechanical heart valve prostheses. Circulation. 1994;89:635-41.
3. Hermans H, Vanassche T, Herijgers P, Meuris B, Herregods M-C, Van de Werf F, et al. Antithrombotic therapy in patients with heart valve prostheses. Cardiol Revi. 2013;21:27-36.
4. Biteker M, Altun I, Basaran O, Dogan V, Yildirim B, Ergun G. Treatment of prosthetic valve thrombosis: current evidence and future directions. J Clin Med Res. 2015;7(12):932.
5. Duran N, Biteker M, Ozkan M. Treatment alternatives in mechanical valve thrombosis. Turk Kardiyoloji Dernegi arsivi: Turk Kardiyoloji Derneginin yayin organidir. 2008;36:420-5.
6. Roudaut R, Serri K, Lafitte S. Thrombosis of prosthetic heart valves: diagnosis and therapeutic considerations. Heart. 2007;93:137-42.
7. Edmunds Jr LH. Thromboembolic complications of current cardiac valvular prostheses. Anna Thorac Surg. 1982;34:96-106.
8. Martinell J, Jimenez A, Rabago G, Artiz V, Fraile J, Farre J. Mechanical cardiac valve thrombosis. Is thrombectomy justified? Circulation. 1991;84:III70-5.
9. Das M, Twomey D, Khaddour AA, Dunning J. Is thrombolysis or surgery the best option for acute prosthetic valve thrombosis? Interact Cardiovascul Thorac Surg. 2007;6:806-11.
10. Melandri G, Vagnarelli F, Calabrese D, Semprini F, Nanni S, Branzi A. Review of tenecteplase (TNKase) in the treatment of acute myocardial infarction. Vascul Healt Risk Managem. 2009;5:249.
11. Kontos Jr GJ, Schaff HV, Orszulak TA, Puga FJ, Pluth JR, Danielson GK. Thrombotic obstruction of disc valves: clinical recognition and surgical management. Annal Thorac Surg. 1989 Jul 1;48(1):60-5.
12. Reddy YS, Pingali K, Otikunta AN, Nathani S, Malladi SR. A study of indications, complications of prosthetic valves and prognosis after treatment of stuck valve. Blood Press;100:80.

13. Patil SN, Ramalingam R, Rudrappa MMB, Manjunath CN. Study of prosthetic heart valve thrombosis and outcomes after thrombolysis. Int J Res Med Sci. 2019;7:1074-8.
14. Gupta D, Kothari SS, Bahl VK, Goswami KC, Talwar KK, Manchanda SC, et al. Thrombolytic therapy for prosthetic valve thrombosis: short-and long-term results. Am Heart J. 2000;140:906-16.
15. Dangas GD, Weitz JI, Giustino G, Makkar R, Mehran R. Prosthetic heart valve thrombosis. Journal of the Am Colleg of Cardiol. 2016;68:2670-89.
16. Lengyel M, Horstkotte D, Voller H, Mistiaen W. Working Group Infection, Thrombosis, Embolism and Bleeding of the Society for Heart Valve Disease. Recommendations for the management of prosthetic valve thrombosis. J Heart Valve Dis 2005;14:567-75.
17. Reyes-Cerezo E, Jerjes-Sánchez C, Archondo-Arce T, García-Sosa A, Garza-Ruiz Á, Ramírez-Rivera A, et al. Fibrinolytic therapy in left side-prosthetic valve acute thrombosis. In depth systematic review. Archivos de cardiologia de Mexico. 2008;78:309-17.
18. Cáceres-Lóriga FM, Pérez-López H, Santos-Gracia J, Morlans-Hernandez K. Prosthetic heart valve thrombosis: pathogenesis, diagnosis and management. Int J Cardiol. 2006;110:1-6.
19. Asante-Korang A, Sreeram N, McKay R, Arnold R. Thrombolysis with tissue-type plasminogen activator following cardiac surgery in children. Int J Cardiol. 1992;35:317-22.
20. Witchitz S, Veyrat C, Moisson P, Scheinman N, Rozenstajn L. Fibrinolytic treatment of thrombus on prosthetic heart valves. Heart. 1980;44:545-54.
21. Sharma V, Singh R, Mishra R, Arora A, Gupta L, Yadava O. Use of tenecteplase for left-sided prosthetic valve thrombosis. JAPI 2012;60:55-8.
22. Özkan M, Kaymaz C, Kirma C, Sönmez K, Özdemir N, Balkanay M, et al. Intravenous thrombolytic treatment of mechanical prosthetic valve thrombosis: a study using serial transesophageal echocardiography. J Am Colleg Cardiol. 2000;35:1881-9.

Cite this article as: Purushotama TS, Sathish K, Santhosh K, Ravindranath KS, Manjunath CN. Efficacy and safety of thrombolytic therapy in prosthetic valve thrombosis. Int J Res Med Sci 2020;8:575-9.