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RESULT OF SLOW INFUSION OF STREPTOKINASE THERAPY IN LEFT SIDED PROSTHETIC VALVE THROMBOTIC OCCLUSION- A CASE SERIES FROM A TERTIARY CARE HOSPITAL IN EASTERN INDIA

Cardiology

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ABSTRACT

Prosthetic valve thrombosis (PVT) is a life threatening complication seen after heart valve replacement and is associated with high mortality and morbidity. Surgical approach or fibrinolysis and heparin therapy are considered as treatments of choice according to the clinical status of the patient. Thrombolytic therapy has been tried in cases with acute prosthetic valve thrombosis as an alternative to emergency operation with variable results. But fear of peripheral embolism has limited its use in left-sided valve occlusions. The incidence of complications decreases with low dose and slow infusion of fibrinolytic therapy. In this study we are presenting our experience of thrombolytic therapy with streptokinase in 40 patients who had presented with acute or subacute left-sided prosthetic valve thrombosis. In this study the mean age was 40.9 years (SD-11.2, range-19 to 64 year) with majority (77.5%) were below 50 year of age. Duration of valve replacement was 2.95 ± 1.74 years (1 to 7 years). Average time of presentation since onset of symptoms was 4.75 ± 2.77 days (1 to 12 days). Majority was presented with NYHA class IV symptoms (22/40) and 50% patients presented with cardiogenic shock. 85% patients had atrial fibrillation and the anticoagulation status was inadequate in 62.5% cases. Overall aortic valve involvement was 37.5% (15 patients) and mitral valve involvement was 62.5% (25 patients). Average mean gradient for aortic valve was 64.5 ±4.2 mm of Hg and that in case of mitral valve was 23.4±3.7 mm of Hg. Duration of thrombolytic therapy was individualized. Average total dose of streptokinase per patient was 25,25000 ± 8,69350 U (ranging from 20,00000 to 50,00000 U) with majority (28/40) had received a total 20,00000U of streptokinase. Patients were re-evaluated after thrombolysis with clinical, echocardiographic, and cine-fluoroscopic evaluation. Total complications (both major and minor bleeding) occurred in 8 patients. Most of them were minor like injection site hematoma, gum bleeding transient GI bleed (hematemesis), hemoptysis and those were resolved spontaneously with conservative management/observational care. Thrombolysis was unsuccessful in 2 patients and death due to massive hemorrhagic CVA occurred in 2 patients. Overall success rate was 90% (36/40). In conclusion, the present study demonstrates the feasibility of thrombolytic therapy for left-sided prosthetic valve occlusion.

KEYWORDS

Prosthetic valve thrombosis, thrombolysis, streptokinase, major and minor bleeding

INTRODUCTION

Rheumatic heart disease remains a major problem in developing countries. Most often valve replacement is needed in cases where the valves are not suitable for either balloon interventional procedures or surgical repair. Prosthetic valve thrombosis (PVT) is a rare but severe complication seen after heart valve replacement and is associated with high mortality and morbidity. The overall incidence of prosthetic valve thrombosis varies from 1% to 13% in mitral and aortic locations[1,2] to as high as 20% in the tricuspid location[3]. It is seen in 0.3–1.3% of prosthetic valves in developed countries[4].

The outcome is mostly fatal without any intervention. Emergency operation with either valve replacement or thrombectomy with debridement was considered the treatment of choice for acute prosthetic valve thrombosis. However, operation in this situation is associated with a high mortality, ranging from 8% to 20.3% for urgent cases and 37.5% to 54.5% for emergency cases[5]. Thrombolytic therapy has been tried in cases with acute prosthetic valve thrombosis as an alternative to emergency operation with variable results [6]. However, studies on large series revealed high risk of emboli, major and minor bleeding, and high mortality rates [7-9]. The incidence of complications decreases with low dose and slow infusion of fibrinolytic therapy [10]. Although thrombolytic therapy has been accepted for routine treatment of tricuspid valve prosthetic occlusions, the concern for potential risk of systemic embolism has limited its use in left-sided prosthetic valve thrombotic occlusions. This study presents the result of slow infusion of streptokinase followed by heparin infusion in 40 cases of left sided acute or subacute prosthetic valve thrombotic occlusion in a tertiary care hospital.

MATERIAL AND METHODS

Forty consecutive patients of left-sided prosthetic valve occlusion with suspected thrombosis admitted to our intensive care unit during a 2-year period from July 2017 to July 2019 and received thrombolytic therapy in the form of streptokinase slow infusion. All patients had baseline electrocardiogram, chest roentgenogram, echocardiogram (M-mode, two-dimensional, and Doppler), cinefluoroscopy and prothrombin time/INR estimation.

Diagnosis

Prosthetic valve occlusion was diagnosed on clinical, echocardio graphic, and cinefluoroscopic criteria.

Clinical: The clinical criteria for prosthetic valve occlusion were recent onset significant dyspnea with orthopnea, cough, and features of acute pulmonary edema, with or without circulatory shock at presentation, and diminished or absent metallic prosthetic valve sounds with or without obstructive murmurs on clinical examination.

Echocardiographic: The presence of a significant pressure gradient (mean pressure gradient of more than 10 mm Hg across the mitral valve and of more than 40 mm Hg across the aortic valve) across the valve by Doppler examination and restricted leaflet excursion noted at either transthoracic or transesophageal echocardiographic examination were taken as criteria for prosthetic valve occlusion. Moderate obstructions (mean PG <10 mm of Hg in mitral and <40 mm of Hg in aortic) were excluded from the study as there may not be acute thrombosis in all cases.

Cinefluoroscopy: The patient was considered to have prosthetic valve occlusion when there was total lack of or marked reduction (reduction in opening angle of each leaflet by at least 25% of the expected) in mobility of one or both leaflets when viewed side-on and face-on in multiple angulated views.

Thrombolytic Therapy

Indication: Thrombolytic therapy was considered for all those patients fulfilling the above criteria for prosthetic valve occlusion.

Thrombolytic agent: Streptokinase was considered if patient had no history of receiving streptokinase or there were no absolute contraindications.

Dose: Streptokinase was given in a bolus infusion of 5,00,000 U over 30 minutes followed by 1,00,000 U/h infusion. The duration of thrombolytic infusion was individualized depending on clinical response as assessed by clinical examination, serial echocardiographic studies, and cinefluoroscopy. According to the study protocol infusion was supposed to give at least for 12 hours but not more than 72 hours. Practically no patient had received infusion for ≥ 45 hours.

Adjuvant therapy: All patients were pretreated with intravenous hydrocortisone- 100 mg; ranitidine- 50 mg; and heparin. All patients received intravenous heparin infusion at a rate of 1,000 U/h after thrombolytic therapy for a variable period until adequate anticoagulation was achieved with oral vitamin K antagonist (target INR 2-3).

Outcome:
The results were interpreted as "success" or "failure" in relation to the clinical outcome and cineradiographic complete opening of valve leaflet and reduction of mean PG (mean PG <10 mm of Hg in mitral and <40 mm of Hg in aortic). Death of the patient, clinical deterioration during thrombolytic infusion, or lack of improvement in objective measurements even after predetermined maximum time of thrombolytic infusion was regarded as "failure". Patients with partial clinical improvement or partial opening of valves with reduction of mean gradient not less than cut off value after strategic time of thrombolytic therapy were excluded from success list and referred to surgery. Patient with significant clinical improvement with mean valvular gradient of 5-10 mm of Hg and 20-40 mm of Hg in case of mitral and aortic valve respectively were kept in success list. But actually in this study, there were no partial success cases after 45 hours of thrombolytic therapy.

Analysis:
All patients were analyzed with regard to clinical presentation, thrombolytic therapy (dose, and duration), immediate results and complication.

RESULTS

Presentation
Forty left sided prosthetic valve thrombosis cases (23 female, 17 male) were admitted over a period of 2 year and thrombolysed with slow infusion of streptokinase. Mean age was 40.9 years (SD-11.2, range-19 to 64 year) with majority (77.5%) were below 50 year of age. Duration of valve replacement was 2.95 ± 1.74 years (1 to 7 years). Average time from onset of symptoms to presentation was 4.75 ± 2.77 days (1 to 12 days). Majority was presented with NYHA class IV symptoms (22/40) and 50% patients presented with cardiogenic shock. 85% patients had atrial fibrillation and the anticoagulation status was inadequate in 62.5% cases.

Prosthetic valve
Among 40 patients 38 (95%) had mechanical prosthetic valve and 2 had bioprosthetic valve. Among mechanical valves 36 had St. Jude bileaflet valves and 2 patients had tilted disc. 8 patients undergone dual valve replacement (mechanical valve in both aortic and mitral) but at the time of presentation thrombosis was involved in one valve only (either mitral or aortic). Overall aortic valve involvement was 37.5% (15 patients) and mitral valve involvement was 62.5% (25 patients). Average mean gradient for aortic valve was 64.5 ±4.2 mm of Hg and that in case of mitral valve was 23.4±3.7 mm of Hg.

Thrombolysis
Thrombolysis done with a single agent (streptokinase) according to the protocol described before. Duration of thrombolytic therapy was individualized based on clinical,echocardiographic, and cine-fluoroscopic evaluation. Average total dose of streptokinase per patient was 25,25000 ± 869350 U (ranging from 20,00000 to 50,00000 U) with majority (28/40) had received a total 20,00000U of streptokinase. 10 patients received total 35,00000U and only 2 had received 50,00000U streptokinase.

Outcome
Outcome was assessed as 'success' or 'failure' as defined before. 28 patients (70%) had achieved success within 1st 15 hours of infusion. Overall success rate was 90% (36/40). Thrombolysis was unsuccessful in 2 cases and 2 patients died due to hemorrhagic complications (CVA).

Complications
Total complications (both major and minor bleeding) occurred in 8 patients. Most of them were minor like injection site hematoma, gum bleeding transient GI bleed (hematemesis), hemoptysis and those were resolved spontaneously with conservative management/ observational care. Major complication like CVA occurred in 2 patients and both of them died due to massive ICH.

Table 1. Complications after streptokinase infusion

Complications	Frequency	Percentage
CVA	2	5%
GI Bleed	3	5%
Gum bleeding	1	2.5%
Hemoptysis	1	2.5%
Hematoma	2	5%
No complications	32	80%

Table 2. Final outcome of streptokinase infusion

Outcome	Frequency	Percentage	Final status
Successful thrombolysis	36	90%	SUCCESS
Failed thrombolysis	2	5%	FAILURE
Death	2	5%	FAILURE

Correlation of different parameters with final outcome
None of the demographic, clinical or patho-physiological factors had a significance correlation with adverse clinical outcome. But total dose of streptokinase was significantly higher in failure group. High dose of streptokinase may increase bleeding risk without promoting any significant benefit.

Table 3. Correlation of different parameters with final outcome

	Success N=36	Failure N=4	P value
Sex distribution	Male 16 Female 20	Male 1 Female 3	0.557
Mean age (years) Mean ± SD	41 ±11.59	39.75±8.1	0.836
Duration after surgery (year)	3.11	1.50	0.078
Type of prosthetic valve Mechanical Bioprosthetic	 33 3	 4 0	0.36
NYHA class	II-4 III-14 IV-18	II-0 III-0 IV-4	3.636
Dose of STK in lacs (mean ±SD)	**23.33±6.32**	**42.5±8.66**	**<0.0001**

DISCUSSION
PVT continues to be a serious complication resulting in high mortality. Despite anticoagulation and improvements in valve design, thrombosis is a lifelong risk with prosthetic heart valves. PVT rate varies depending on several factors. These include the type, generation, and thrombogenicity of the valve. Additionally, location of the valve, intensity of anticoagulation, and multiple clinical risk factors (atrial fibrillation, congestive heart failure, coronary artery disease, hypercoagulopathy, cancer, dehydration, infection, etc.) also contribute to the PVT rate.[11] Among these predisposing factors, inadequacy of anticoagulation is the most important one. In this case series, anticoagulation was found to be inadequate in 62.5% cases. Similar thing was reported by Reddy et al[12]. who had found inadequate anticoagulation in 70% patients.

25% of the patients in this series presented within 1 year of operation. Miller et al.[13] previously have shown that the incidence of thromboembolism was highest during the first postoperative year. In the series reported by Roudaut et al.[4] 45% of the patients presented within 2 years of operation. However, the risk of thrombosis continues forever, as evident in this study, 22.5% patients had presented 5 years after the operation.

There is no particular guideline for thrombolysis protocol in PVT. Generally 2 types of thrombolytic strategy with streptokinase are commonly followed. Either a standard infusion of streptokinase (0.25 MU over 30 min, followed by 0.1 MU/hour for 72–96 hours) or an

accelerated infusion (1.5 MU over 1 hour). O¨zkan et al.[10] performed five different thrombolytic treatment strategies in patients with PVT. These regimens included rapid streptokinase (1.5 MU/3 h), slow streptokinase (1.5 MU/24 h), high dose rt-PA (100 mg, 10 mg bolus, 90 mg/5 h), half-dose slow infusion rt-PA (50 mg/6 h), and low-dose slow infusion rt-PA (25 mg/6 h). Treatment success did not differ between the groups. However, the complication rate was found to be significantly lower in the slow infusion low-dose rt-PA group than in the other groups. In this present case series we had slightly modified the infusion protocol of streptokinase (0.5 MU over 30 min, followed by 0.1 MU/hour. We didn't continue infusion for ≥ 45 hours as with that dose (total 5 MU) 1 patient expired due to CVA and 1 patient was taken to emergency surgery as there was clinical deterioration (persistent shock). Another patient was also transferred to CTVS for the same reason after 30 hours of infusion. 1 patient had got CVA with 30 hours of infusion. Overall thrombolysis was successful in 90% patients (36/40) which were almost similar to other recent case series but complications are lower than those studies.

Gupta et al.[8] reported a series of 110 patients with obstructive PVT undergoing thrombolysis. According to this study, 108 patient received standard streptokinase protocol (250,000 U in 30 min, followed by 100,000 U/h), and two received urokinase. Complete hemodynamic improvement was observed in 81.8% (90/110) of the patients, and partial improvement in 10%. There were 19.1% embolic episodes, 19% bleeding, and 7.3% deaths during therapy. Roudaut et al.[4] reported their study of 127 instances of non-obstructive PVT treated with fibrinolysis. Complete resolution of hemodynamic abnormalities was seen in 70.9% and partial resolution in 17.2%. The rates of major bleeding, systemic embolism, and mortality rate were reported as 4.7%, 15%, and 11.8%, respectively. There were no significant differences in the rates of complications among different agents employed. These results are close to those of the study of Gupta et al.[8] Karthikeyan et al.[9] randomized 120 patients with PVT. The patients received either a standard infusion of streptokinase (0.25 MU over 30 min, followed by 0.1 MU/h 72–96 h) or an accelerated infusion (1.5 MU over 1 h). Death, major bleeding, and systemic embolism occurred in 16.7% of the patients. Death (5% vs. 4%), major bleeding (7% vs. 4%), minor bleeding (8% vs. 5%), and systemic embolism (4% vs. 2%) did not differ significantly between treatment groups. In these studies, fibrinolytic therapy was associated with high complication rate but there were no significant differences in complications among the different strategy of the same agents employed. In current study death, major and minor bleeding occurred in 5%, 5% and 15% of cases respectively. The total dose of streptokinase is significantly higher among death or major bleeding cases "failure" group compared to "success" group (p value <0.0001).

Thrombolysis was ineffective in 5% patients of current study. The reason may be formation of organized white-gray pannus on both disc and struts. Where pannus is the likely cause of occlusion, thrombolytic therapy is unlikely to succeed. Similarly, if there is a combination of pannus and thrombus, thrombolytic therapy can result in only a partial success.

Limitation

Major pitfall of this study was small number of cases. Long term follow up was not included in study protocol. So, partial success cases with underlying pannus or could not be followed up or chance of reocclusion could not be assessed for long term duration.

CONCLUSION

Thrombotic occlusion of prosthetic valves is a potentially life-threatening complication that needs prompt attention. Inadequate anticoagulation is common and one of the potential risk factors for it. Thrombolytic therapy is feasible and associated with high initial success rate. Slow infusion of thrombolytic therapy has low complication rate but prolonged infusion of streptokinase (high total dose) is associated with adverse outcome. Large randomized controlled trials are needed to determined optimum dose and duration of thrombolytic therapy.

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