



THROMBOLYTIC THERAPY WITH STREPTOKINASE IS EFFECTIVE AND SAFE IN MECHANICAL PROSTHETIC VALVE THROMBOSIS

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ABSTRACT

Background: Thrombolytic therapy is a safe and effective alternative to surgery in treatment of mechanical prosthetic valve thrombosis. In limited resource nations streptokinase as an thrombolytic agent has been used successfully for a prolonged period. Our study aimed to evaluate efficacy and safety of thrombolytic therapy with streptokinase. **Methods:** This is a prospective observational single centre study carried out between May 2015 to April 2020 at SCB Medical College, Cuttack, Odisha, a tertiary care hospital in eastern India. Patients with history of valve replacement with mechanical prosthetic valve, presenting with symptoms and signs suggestive of valve thrombosis were analyzed. 147 consecutive patients (109 females 38 males, mean age 35.5 +/- 11.6 years) of obstructive PVT (130 mitral, 17 aortic) thrombolysed with streptokinase according to a specified protocol of prolonged infusion. Serial echo Doppler parameters were monitored in all patients to guide the duration of treatment and to quantify its efficacy. Hundred and twenty eight of the 139 survivors of the index episode were followed up for a mean period of 28.6 +/- 10.8 months. **Results:** Most patients were in NYHA II (55,37.4%) and III (59,44.1%), 58(39.5%) in atrial fibrillation, 78(53.1%) had INR less than 2 and 114(77.6%) presented with in 14 days of symptoms. Mitral prosthesis was involved in 130 patients ie 88.4% (74.8% + 13.6%), followed by aortic in 17(11.6%) (6.8% + 4.8%). Clinical success was present in 128(87.1%) mostly with in 24 hours(101,68.4%) of streptokinase infusion. 8(5.4%) patients had in hospital death, 12 had CVA, 6 peripheral embolism, 2 upper GI bleed, 2 large subcutaneous hematoma and 12 minor complications. **Conclusion:** Thrombolytic therapy with streptokinase is an effective and safe alternative to surgery in obstructive thrombosis of mechanical prosthetic valve

KEYWORDS

INTRODUCTION

Rheumatic heart diseases are the most frequently encountered valvular heart disease in developing countries and often require surgical replacement with prosthetic valves. Prosthetic valve thrombosis (PVT) is a life threatening complication and its management is difficult. The incidence of mechanical valve thrombosis of left-sided valves is 0.3% to 1.3% per patient-year in developed and up to 6% in developing countries and up to 20% of tricuspid valves.¹

Bioprosthetic valve thrombosis is less common, incidence being 0.03% to 0.5% per patient year.² The risk of PVT depends on valve type, valve position, anticoagulation status, the presence of prothrombotic states such as pregnancy, atrial fibrillation, and/or ventricular dysfunction. The most common cause of PVT is inadequate anticoagulant therapy.³ PVT has been divided into two types, obstructive PVT (OPVT) and non-obstructive PVT (NOPVT). Patients with NOPVT present with minimal clinical symptoms and they are stable but they constitute a group of high embolic potential.⁴ OPVT can present with a wide spectrum of symptoms, and should be suspected by symptoms of acute onset breathlessness, fatigue, thromboembolism or low cardiac output with decrease in intensity of valve closure sounds (mechanical valves), new and pathologic murmurs or documentation of inadequate anticoagulation.⁵ Thrombosis is more common in mitral and tricuspid position than aortic. Cine fluoroscopy (CF) and TTE are quick, effective, and complementary diagnostic tools to diagnose PVT in most patients, transesophageal echocardiography (TEE) helps further in confirming the diagnosis and planning management.⁶ Multidetector computed tomography is emerging as a diagnostic modality with probably more

precision for differentiating between pannus and thrombus.⁷ Efficacy of thrombolytic therapy with streptokinase was first reported by Luluaga et al in 1971.⁸ Since then streptokinase has remained as the main treatment option in developing countries. There are a lack of randomized controlled prospective trials comparing surgical and thrombolytic therapies in PVT, but it is shown that intravenous slow infusion thrombolysis (tenecteplase) given in discrete, successive sessions guided by serial transesophageal echocardiography (TEE) can achieve a high rate of success with a low risk of complications and even in patients with New York Heart Association (NYHA) class III or IV.^{9,2014 ACC/AHA practice guidelines} states that

1. Fibrinolytic therapy is reasonable for patients with a thrombosed left-sided prosthetic heart valve, recent onset (<14 days) of NYHA class I to II symptoms, and a small thrombus (<0.8 cm²). (Class IIa, Level of Evidence: B)
2. Fibrinolytic therapy is reasonable for thrombosed right-sided prosthetic heart valves. (Class IIa, Level of Evidence: B)
3. Emergency surgery is recommended for patients with a thrombosed left-sided prosthetic heart valve with NYHA class III to IV symptoms. (Class I, Level of Evidence: B)
4. Emergency surgery is reasonable for patients with a thrombosed left-sided prosthetic heart valve with a mobile or large thrombus (>0.8 cm²). (Class IIa, Level of Evidence: C)
5. Some patients with no or minimal symptoms and small thrombi can

be managed by unfractionated heparin alone, converted to fibrinolytic therapy if unsuccessful.

2017 ACC/AHA focused update of 2014 ACC/AHA practice guidelines :- Urgent initial treatment with either slow-infusion low-dose fibrinolytic therapy or emergency surgery is recommended for patients with a thrombosed left-sided mechanical prosthetic heart valve presenting with symptoms of valve obstruction (Class I B).¹⁰

2017 ESC guidelines, on the other hand, recommend emergency valve replacement for obstructive prosthetic valve thrombosis in critically ill patients without a contraindication to surgery, and recommend standard dose of fibrinolytic therapy (Class IIA) when surgical risk is deemed high/not available or for right-sided valve thrombosis.¹¹

Management of non-obstructive mechanical prosthetic valve thrombosis depends mainly on the occurrence of a thromboembolic event and the size of the thrombus. Surgery should be considered for a large (>10 mm) non-obstructive prosthetic valve thrombus complicated by embolism or which persists despite optimal anticoagulation. Fibrinolysis may be considered if surgery is at high risk but carries a risk of bleeding and thromboembolism.

The choice of thrombolytic versus surgical approach should be individualized and based on a multidisciplinary team discussion after carefully weighing the risks and benefits of each approach.¹²

METHODS

This is a prospective observational single centre study carried out between September 2015 to April 2020 at SCB Medical College, Cuttack, Odisha, a tertiary care hospital in eastern India. Patients with history of valve replacement with mechanical prosthetic valve, presenting with symptoms and signs suggestive of valve thrombosis between Sep 2015 and April 2020 were analyzed. Detail routine haematological and biochemical investigations, PT INR, ECG, X-ray chest PA view and transthoracic echocardiography (TTE) was done in all patients. If findings in TTE raised suspicion of stock valve, transesophageal echocardiography (TEE) and cine-fluoroscopy was performed before administering thrombolytic therapy except those who were very sick particularly if in frank pulmonary edema or cardiogenic shock.

Details of prosthetic valve, its model, size and position were collected from patients records and noted down in bed head ticket. Details of patients symptoms and signs including symptoms duration, palpitation, breathlessness, NYHA class, embolic phenomenon (cerebral, peripheral, coronary), history of syncope and prosthetic valve sounds were recorded.

TREATMENT PROTOCOL AND EVALUATION OF OUTCOME

Intravenous thrombolysis was given using streptokinase (STK) as the lone thrombolytic agent to all patients. 250,000 unit of STK was given over 30 minutes followed by 100,000 U/hour. STK was administered until valve reopening, complications or for at least 48 hours. IV heparin infusion was started after thrombolysis. After stabilization concomitant oral anticoagulant (vitamin K antagonist warfarin or acenocoumarole) was administered to achieve target international normalised ratio (INR) levels. Heparin was discontinued 24 hours after achieving target INR. And in addition all patients were started on aspirin 75 mg/day.

Each patient underwent TTE evaluation every 12 hour from start of thrombolytic therapy and daily thereafter if full valve reopening was not achieved. Clear cut movement of both leaflets in a paralld fashion and 50% decrease in trans-valvular gradient indicate valve reopening. This is confirmed by fluoroscopy which was performed in each patient 24 hour after completion of thrombolytic therapy. Complications if any were recorded and further investigations and treatment done.

FOLLOWUP

At the time of discharge detail instructions regarding importance of anticoagulation regimen timing of VKA intake and its interaction with food and other drugs were given to each patient. Each patient was advised to do PT INR at regular interval and also explained about signs and symptoms of valve thrombosis. They were advised to report immediately if symptomatic and/or PT INR is not in therapeutic range. Follow up in cardiology OPD was advised at 1 month, 3 months and

3 monthly thereafter.

STATISTICAL ANALYSIS

Continuous variables were presented as mean $\pm$ standard deviation and categorical variables as counts and percentages. All data were analysed using the Statistical Package for Social Sciences (SPSS; Chicago, IL, USA) program, version 15.

RESULTS

147 patients with prosthetic valve thrombosis were identified and analyzed in this 5 years study. Mean age of the patients was 35.5 $\pm$ 11.6 years, of which 110(74.8%) were below 40 years of age. Majority of the patients were females (109, 74.1%). All patients were of rheumatic heart disease. Most of the patients presented with NYHA class II (55,37.4%) and III (59,40.1%) symptoms (Table 1). All patients presented with symptoms. Most patients (114, 77.6%) had symptom duration less than 14 days. Fifty eight patients (39.5%) had atrial fibrillation (AF) at presentation. Of these, 7 patients had recent onset AF.

Majority of patients (77; 52.4%) presented after five years of surgery. Mitral prosthesis was involved in 88.4% (74.8% + 13.6%), followed by aortic in 11.6% (6.8% + 4.8%) (Table 2). Details of valve types are mentioned in table 2. Acenocoumarol was the most commonly prescribed anticoagulant, followed by warfarin. In addition 26.4% of patients were taking aspirin. Majority of the patients (78,53.1%) had INR in non-therapeutic range (<2). Eighty eight(59.9%) patients were poorly compliant with drugs and monitoring of prothrombin time.(Table-3) More patients from rural background and in economically underprivileged groups had poor compliance to medications.

All patients were thrombolysed with streptokinase. The regimen in our study was a 250000 units bolus, followed by 100000 units per hour infusion till clinical response. Infusion was stopped if there was no response to treatment after 48hours. Clinically success was achieved in 130(88.4%) patients.(Table 4) Duration of lysis was less than 24hours in most of the patients (101,68.4%). All 4 patients with pregnancy tolerated streotokinase and had favourable clinical outcome.

Details of complications are mentioned in table 5. Eight (5.4%) patients had in hospital death, 6 due to acute pulmonary edema & cardiogenic shock and 2 following intracerebral bleed. During the follow-up period 15(10.2%) patients had recurrence of thrombosis in the same prosthetic valve; 10 of them re thrombolysed (one died of cerebral hemorrhage), 2 died shortly after presentation due to acute pulmonary edema, 3 underwent re valve replacement one of them died post op during hospital stay.

DISCUSSION

Many patients of rheumatic valvular heart disease during their lifetime need valve replacement as a definitive treatment. All patients with mechanical PV and bio-prosthetic valve with h/o thrombo-embolism need anticoagulation for whole life after the replacement. PVT though not very uncommon, may be fatal if not diagnosed and treated timely. The traditional treatment for the management of PVT has been thrombectomy or re-valve replacement, which incurs a major limitation of high surgical mortality. It has led to an increased usage of thrombolysis in recent years, 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 streptokinase and effect was monitored by echocardiography. 13-14

In this single center study experience of 147 cases of mechanical PVT treated over a period of 60 months has been reported. In this study more (74.1%) patients were women as in many other studies from India. 15-18 Mitral valve prosthesis was most commonly involved in the majority of the patients (88.4%) compared to aortic valve prosthesis (11.6%) which is similar to many studies from India and other countries. 15-20

In this study prothrombin time was below therapeutic range in 53.1% of patients, overall 59.9% of patients were poorly compliant with anticoagulants and monitoring of prothrombin time. Many of them were irregular in taking medications and monitoring of PT INR due to ignorance, negligence, non availability test in many places(rural area) and financial constraints. In a recent study by Karthikeyan G et al, 72%

(79/110) of the patients had inadequate anticoagulation at presentation.13 This highlights the problems of valve replacement in developing countries with economically under privileged population particularly in rural area.

Clinical success was achieved in 87.1% mostly with in 24 hours of streptokinase infusion. 12.3% had embolic complications and 5.4% died during hospital stay. Success rate with fibrinolytic therapy using streptokinase varies from 73% to 90.2% in different studies. 10-17 Other studies have shown an embolic events in 8% to 17% of cases following thrombolysis.15,16

CONCLUSION

Thrombolytic therapy with streptokinase is effective and safe in treatment of prosthetic valve thrombosis with varied presentation. Presence of atrial fibrillation and non compliance of anticoagulant medications were common in patients with PVT. All patients with valve replacement should be counseled regarding continuation of anticoagulant following surgery and periodic monitoring for its therapeutic dose to prevent PVT particularly if the patient belongs to educationally economically underprivileged community from rural background.

Table 1 – Patient characteristics (n = 147)

Age mean (SD) in years	35.5(11.6)
Less than 40 years	110 (74.8)
40 or more years	37 (25.2)
Male - n (%)	38 (25.9)
Female – n (%)	109 (74.1)
AF	58 (39.5)
DM	9 (6.1)
Anemia	12 (8.2)
Renal dysfunction	4 (2.7)
Pregnancy	4 (2.7)
Symptoms duration	
Less than 14 days	114 (77.6)
14 days or more	33 (22.4)
NYHA class	
I	8 (5.4)
II	55 (37.4)
III	59 (40.1)
IV	14 (9.6)
Acute pulmonary edema/ Cardiogenic shock	11 (7.5)

Table-2 Patients characteristics related to valve

Time since valve replacement	
<1 year n(%)	11 (7.4)
1-3 years n(%)	26 (17.8)
3-5 years n(%)	33 (22.4)
>5 years n(%)	77 (52.4)
Prosthetic valve position	
Mitral	110 (74.8)
Aortic	10 (6.8)
DVR Mitral	20 (13.6)
DVR Aortic	7 (4.8)
Prosthetic valve type	
St Jude	38 (25.9)
Medtronic	33 (22.4)
TTK Chitra	55 (37.4)
Bioprosthetic	2 (1.4)
Others	19 (12.9)

Table- 3: Anticoagulant Status

Anticoagulant type	Number	Percentage
Acenocoumarol	79	53.7%
Warfarin	68	46.3%
Drug compliance		
Good	59	40.1%
Poor	88	59.9%
INR		
<2	78	53.1%
2 - 3	65	44.2%
>3	4	2.7%

Table-4 Results of Thrombolysis

Clinical success (n (%))	130 (88.4)
Duration of thrombolysis	
<12 hours	15 (10.2)
12-24 hours	86 (58.5)
24-48 hours	46 (31.3)

Table-5: MAJOR COMPLICATIONS

Death	8 (5.4)
CVA (Infarct)	7 (4.8)
CVA (Intracerebral bleed)	5 (3.4)
Peripheral embolism	6 (4.1)
GI Bleed	2 (1.4)
Large sub cut hematoma	2 (1.4)

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