Original Article

Tenecteplase versus streptokinase thrombolytic therapy in patients with mitral prosthetic valve thrombosis

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ABSTRACT

Objective: Prosthetic valve thrombosis (PVT) is a dreadful complication of mechanical prosthetic valves. Thrombolytic therapy (TT) for PVT is an alternative to surgery and currently making a leading role. This study compares TT with tenecteplase (TNK) and streptokinase (SK) head to head in patients with mitral PVT.
Methods: In this single center, observational study, patients with mitral PVT diagnosed by clinical data, transthoracic echocardiography, transesophageal echocardiography, and fluoroscopy were included. After excluding patients with contraindications for thrombolysis, they were randomly assigned to receive either SK or TNK regimen. Patients were monitored for success or failure of TT and for any complications.
Results: Among 52 episodes (47 patients with 5 recurrences) of mechanical mitral PVT, 40 patients were thrombolyzed with SK and 12 patients were thrombolyzed with TNK. Baseline characteristics including demographic profile, clinical and echocardiographic features, and valve types were not statistically significant between the groups. Complete success rate was 77.5% in SK group and 75% in TNK group (p = 0.88). Partial success rate, failure rate, and major complications were not statistically significant between the two groups. Within 12 h of therapy, TNK showed complete success in 33.3% of patients compared to 15% in SK group (p-value <0.02). Minor bleeding was more common in TNK group.
Conclusion: Slow infusion of TNK is equally efficacious but more effective than SK in the management of mitral mechanical PVT. 75% to 77.5% of PVT patients completely recovered from TT and it should be the first line therapy where the immediate surgical options were remote.
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1. Background

Prosthetic valve obstruction by thrombosis is a rare but serious complication which occurs in 0.5% to 8% of the left-sided mechanical prosthetic valves.[1] In India, the incidence of prosthetic valve thrombosis (PVT) is high, with 6.1% in the first 6 months after replacement of the valve.[2] High mortality rate was reported with urgent surgery in certain subsets of patients of PVT compared with thrombolytic therapy (TT).[3] Intravenous TT for PVT has been used as an alternative to surgical treatment and currently making a leading role in the management of PVT.[4] Thrombolytic regimens of common thrombolytic agents used in previous studies showed different outcomes and various degree of safety in the treatment of PVT. However, comparative study of thrombolytic regimen of tenecteplase (TNK) with streptokinase (SK) was not done in patients with PVT. This study was done to compare the efficacy and safety of TNK thrombolytic regimen with SK thrombolytic regimen in the management of patients with mechanical mitral PVT.

2. Methods

This study was done in a tertiary care hospital during August 2014 to October 2016 after getting ethical committee approval.

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Forty-seven patients with 52 episodes (5 recurrent PVT) of mitral PVT diagnosed by clinical data, transthoracic echocardiography (TTE), transesophageal echocardiography (TEE), and fluoroscopy in whom surgical treatment was not possible were included in this study after obtaining informed consent. A detailed history of presenting symptoms and their duration, time of mitral prosthetic valve replacement, drug compliance, and frequency of INR monitoring were enquired and analysed. Clinical examination was done for the presence of prosthetic valve click, murmur and lung signs.

Echocardiography:

- Thrombus was recognized as soft and homogeneous, mobile or fixed echo densities located at the valve occluder and/or valve struts. Thrombus mobility and dimensions were measured. Patients with thrombus size of >1 cm^2 were excluded.
- Pressure gradient (PG) across the prosthetic valve was compared with previous baseline value. False causes of increased PG [e.g. increased flow across the valve due to tachycardia, anemia, and regurgitation) were excluded by measuring pressure half-time ($P^1/_2T \geq 150$ msec was considered as obstructed valve).
- If baseline value was not available, then the Doppler mitral valve area of ≤ 1.5 cm^2 and prosthetic mitral valve mean gradient of ≥ 10 mmHg were taken as prosthetic valve occlusion.[5]

TEE was used whenever TTE images were inadequate. Fluoroscopy was used as an additional tool to diagnose prosthetic valve thrombotic obstruction. Reduced or fixed mobility of leaflets was documented (Examples: Figs. 1–6).

Patients presenting with cardiogenic shock with multi-organ dysfunction, prosthetic valve obstruction by pannus and contra-indications to use of thrombolytic therapy like, active internal bleeding, history of hemorrhagic stroke, recent cranial trauma or neoplasm were excluded. Prothrombin time (PT) and International Normalised Ratio (INR) were measured on the day of admission. Blood culture and sensitivity with other routine blood investigations were done.

Patients were randomly assigned to receive either SK regimen (2.5 lakh IU intravenous bolus for 30 min followed by 1 lakh IU/hr intravenous infusion for 24 h)[6] or TNK regimen (0.5 mg/kg as intravenous infusion over 24 h)[7] and thrombolysis was repeated up to 3 times (72 h) in SK regimen and 2 times (48 h) in TNK regimen for obtaining normal or near normal reduction of mitral valve pressure gradient. Patients were monitored for success or failure of hemodynamic improvement by serial TTE for every 6 h and for any complications. Routine blood investigations along with PT, INR, and culture and sensitivity for patients with fever were done at the time of admission. Complete success was defined as normal or near
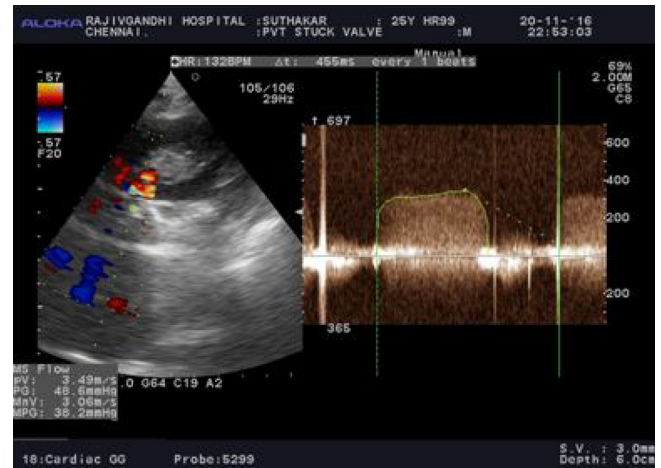

Fig. 1. A patient with obstructive mitral PVT. TTE of parasternal short axis view showed medial leaflet of mitral bileaflet valve was stuck in closed position and lateral leaflet was moved to open position during diastole.

Fig. 2. Continuous Doppler across the mitral prosthesis of patient shown in Fig. 1: Peak PG was 48.6 mmHg and mean PG was 38.2 mmHg.

Fig. 3. Fluoroscopy showed the same leaflet was immobile in RAO caudal view of patient shown in Fig. 1 before TT.
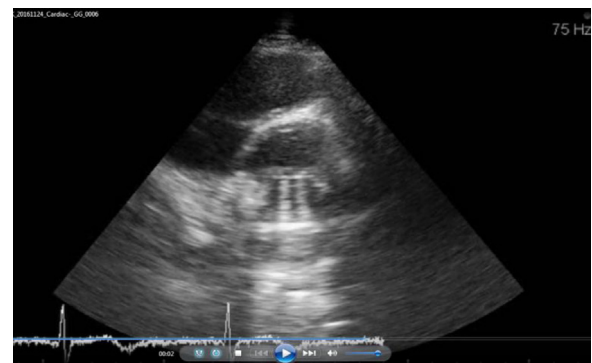

Fig. 4. After thrombolytic therapy of patient shown in Fig. 1, TTE parasternal short axis view showed both leaflets of mitral PV in open position during diastole.
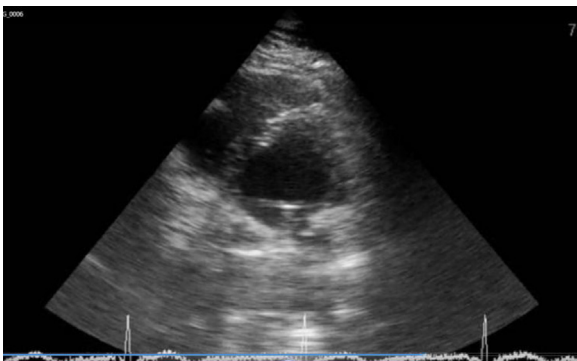
normal transvalvar gradient and restoration of normal leaflet motion on fluoroscopy without any major complications.[6] Partial success was defined as reduction of > 50% of transvalvar gradient from the baseline or complete hemodynamic response with major complication or restricted movement of prosthetic valve leaflets on cinefluoroscopy even though the transvalvar gradients completely normalized.[6] Failure of TT is defined as no hemodynamic response
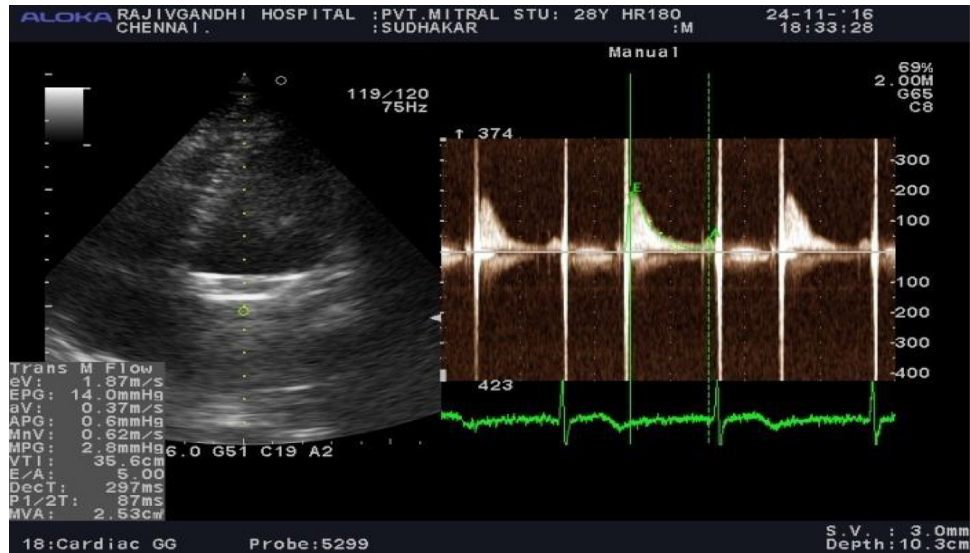
Fig. 5. Pressure gradient across the mitral PV of Fig. 1 patient became normal after the thrombolytic therapy, mean gradient was 2.8 mmHg.
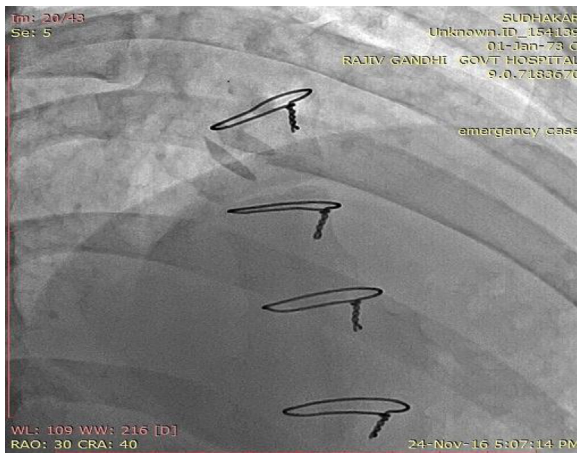

Fig. 6. Fluoroscopy image showed both leaflets of mitral prosthetic valve were in opened position in diastole after TT.

even with extended thrombolysis (upto 72 h) or death by major complications.[6] After successful thrombolysis, Inj. Heparin 16 IU/kg/hr by intravenous infusion for initial 48 h followed by 70 IU/kg intravenous QID and Acenocoumarol according to activated partial thromboplastin time and PT INR, respectively. Aspirin was added at a dose of 75 mg daily. Heparin and Acenocoumarol therapy were continued until PT INR fell in therapeutic range of 2.5–3.5. Complications were managed according to standard treatment protocol. Data were analyzed by Chi-square test and probability value of <0.05 was taken as significant.

3. Results

In this study, 47 patients with 52 episodes of mitral PVT were included. Among the 47 patients 28 were men (59.6%) and 19 were women (40.4%). Their mean age was 33 ± 19 years (range 14 yrs to 52 yrs). INR was subtherapeutic in 90.3% of patients. All the patients were presented with dyspnea of NYHA class III or IV. Duration of dyspnea ranged from 2 days to 2 weeks. Only 2 patients had fever. Poor drug compliance was present in 43 (83%) of 52 episodes. Types of mitral mechanical prostheses were bileaflet (St Jude − 39, Sorin −1) in 40 episodes and tilting disc (TTK Chitra)

in 12 episodes. 40 patients received SK and 12 patients received TNK. Baseline characteristics including sex, age, time from valve replacement, NYHA class, previous presence of atrial fibrillation, stroke, previous aspirin use, clinical presentation, type of mitral valve, number of prosthetic valves implanted, and mean pressure gradient at presentation had no statistical difference between SK and TNK groups (Table 1).

Complete success was observed in 77.5% in SK group and 75% in TNK group (p- value 0.88). Within 12 h of therapy, TNK showed complete success in 33.3% of patients compared to only 15% in SK group (p-value <0.02). The mean duration of complete successful thrombolytic therapy was 21.40 h with SK and 15.20 h with TNK. In SK group, 28 out of 31 patients (90%) needed up to 24 h infusion for successful lysis and only 3 (10%) patients required TT for more than 24 h (that is extended lysis up to 42 h) to get successful thrombolysis. All the 9 patients in TNK group needed up to 24 h infusion to get successful thrombolysis. (Table 2).

Partial success rate was 20% (8 pts) in SK group and 25% (3 pts) in TNK group (p-value = 0.5). Partial success patients were given 3

Table 1
Baseline characteristics of patients with mitral PVT.

Baseline characteristics			
Demographic profile	SK	TNK	p-value
Sex: Total Episodes [Male/Female]	40 [22/18]	12 [8/4]	0.47
Number of patients[Male/Female]	21/18	7/1	
Recurrence[Male/Female]	1/0	1/3	
Age in yrs	33 ± 19	28.5 ± 6.5	0.06
Time from valve replacement (yrs)	4.86	4.5	0.93
NYHA class III-IV	40	12	1.00
AF	12	2	0.47
Stroke	1	0	0.49
Aspirin use	6	3	0.50
Clinical presentation			
Dyspnea	40	12	1.00
Absent valve clicks	40	12	1.00
Type of mitral prosthetic valve			
Bileaflet (St Jude, Sorin)	31	9	0.94
Single leaflet (TTK)	9	3	0.88
Double valve implanted (Aortic and Mitral)	1	1	0.38
Echocardiographic features			
Initial Mean gradient (mmHg)	28.3	27.6	0.93

Table 2
Duration of thrombolytic therapy of patients with complete success in SK and TNK groups.

Time for successful lysis	SK		TNK	
	Number of pts.	Total lysis time (hrs)	Number of pts.	Total lysis time (hrs)
6 h	2	12	2	12
12 h	4	48	2	24
18 h	4	72	3	54
24 h	18	432	2	48
30 h	1	30	0	0
36 h	1	36	0	0
42 h	1	42	0	0
48 h	0	0	0	0
Total	31	672	9	138
Mean time for successful lysis		21.40		15.20

cycles of SK therapy and 2 cycles of TNK therapy in respective groups but did not show any hemodynamic improvement even after repeated cycles (Table 3). Patients with partial success were referred to undergo redo mitral valve replacement.

Only one patient died in SK group due to sudden cardiac death. 5 patients (12.5%) of SK group had embolic stroke and 1 patient (8.3%) of TNK group had left radial artery occlusion (p = 0.005). Among the 6 patients with embolic complications, only 2 patients were in atrial fibrillation. The incidence of embolic stroke was higher in SK group than TNK group (p = 0.0006). Overall embolic complications were not statistically significant between SK and TNK (p = 0.38). Minor bleeding rate was more common in TNK group (p = 0.00008) (Table 4).

4. Discussion

Therapy for PVT includes anticoagulation with heparin, thrombolysis with fibrinolytics, and surgical valve replacement. Management of PVT is mainly influenced by the valve location and presence or absence of valve obstruction. Between 1990 and 2015, several series of cases diagnosed as PVT and treated with thrombolysis have been published in India with a total number of 413 patients reported with an acceptable initial success rate of 81.1%.[2] Surgical valve replacement for PVT has been associated with a significant risk of mortality.[3] Castilho et al reported significant increased risk of mortality with surgery when compared with TT.[8] Hence, there is a need of an effective and promising treatment strategy for PVT in developing countries like India. Previous studies of TT in PVT showed promising results suggesting this modality would be the first line of management, but randomized controlled trials are lacking. Even though the evaluation of seven studies by Karthikeyan et al[9] showed no difference in main outcome (restoration of valve function) between patients treated surgically (446 patients) and medically by TT (244 patients), recent reports from two studies have shown the leading role of TT in PVT management.[1,10] The limited availability and high cost of surgery have turned TT into the initial choice of therapy for PVT in most developing countries. Various thrombolytic regimens of common thrombolytic agents like SK, tissue plasminogen activator, and TNK used in previous studies showed different outcomes with varying degrees of safety in the treatment of PVT. Single case reports have shown that TNK was

used successfully by slow infusion[7] as well as bolus[11–14] in the TT of mitral PVT. TNK was given as intravenous bolus dose (1 mg/kg) for left sided PVT of 10 cases and showed a complete success rate of 100% by Sharma et al[13] However, comparative study of thrombolytic regimen of TNK with SK is lacking. In our study, we used TNK as slow intravenous infusion for mitral PVT to compare with SK therapy. Slow infusion of TNK was used to avoid sudden dislodgement of large thrombus material leading to massive systemic embolism.

Number of patients receiving SK was higher than TNK in this study because of immediate availability of the thrombolytic agent SK at the time of initiating treatment. The occurrence of PVT was commonly due to poor drug compliance by the patients (83%) and maintaining a subtherapeutic level of INR (90.3% of patients). Only 9 (17%) out of 52 patients received aspirin along with anti-coagulants. Presence of atrial fibrillation, previous stroke, and type of prosthetic valve did not alter the success rate and outcome of therapy with TNK or SK.

Complete and partial success rates were almost equal in both groups. But, TNK showed complete success in 33.3% of patients within 12 h of starting TT when compared to SK (15%). Mean time for successful lysis with TNK was approximately 5 h lower than SK.

Table 4
Complications of thrombolytic therapy in SK and TNK groups.

Complications	SK (%)	TNK (%)	p-value
Death	1 (2.5)	0	0.12
Embolic events			
Stroke	5	0	0.0006
Limb ischemia	0	1	0.005
Total	5 (12.5)	1 (8.3)	0.38
Bleeding (Major)	0	0	
Bleeding (Minor)	0	2 (16.7)	0.00008

Table 3
Success rates of thrombolytic therapy in SK and TNK groups.

Thrombolytic Success	SK (%)	TNK (%)	p value
Complete success	31 (77.5)	9 [75]	0.88
Partial success	8 [20]	3 [25]	0.50
Failure of TT	1 (2.5)	0 [0]	0.11
Complete success within 12 h	6 [15]	4 (33.3)	0.02

Fig. 7. Thrombolytic success rates of mitral PVT in SK and TNK groups.

The incidence of embolic stroke was higher in SK group than TNK group (p = 0.0006). This denotes that the TNK is more effective than SK. (Fig. 7) In few patients, successful lysis occurred at a maximum of 42 h of SK therapy and 24 h of TNK therapy. Prolonged or repeated infusion of thrombolytics more than these limits did not show any improvement in outcome.

The increased fibrin specificity and increased resistance to plasminogen activator inhibitor-1 (PAI-1) may be the reason for effectiveness of tenecteplase. Failure rate and overall complication rate were not statistically significant between the two groups. Patients with partial success were considered and motivated for redo mitral valve replacement surgery. No major bleeding complications were noted with both thrombolytics, but minor bleeding was more common in TNK group. TT should be the first line of management of mitral PVT in developing countries like India where the immediate surgical options were remote. TNK can be used for TT of mitral PVT in place of SK with equal efficacy and at the same rate of complications.

5. Limitations of the study

This study was a single center, non-randomized and observational study which included relatively small number of patients in both TNK and SK groups. The number of patients in TNK group was 3 times lower than the SK group. This study only compared the effects of two fibrinolytics alone and not the surgical treatment of mitral PVT with TT.

6. Conclusion

In this study, we have evaluated the common reasons for the occurrence of PVT in mechanical valves, which are poor drug (oral anticoagulants) compliance, and poor INR monitoring by the patients. The type of valves implanted and presence or absence of atrial fibrillation did not have an impact on increasing the chance of PVT. 75% to 77.5% of patients completely recovered from PVT by TT and it should be the first line of management of mitral PVT in developing countries like India where the immediate surgical options were remote. The complete and partial success rates of TT with TNK in mitral PVT were equal to SK. Slow infusion of TNK for mechanical mitral PVT was more effective within 12 h of starting the treatment than SK therapy. This slow infusion regimen of TNK is an alternative to SK in the management of mechanical mitral PVT when SK is contraindicated or when immediate effect is required.

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