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Original Research Article

Comparative safety and efficacy of tenecteplase and streptokinase in prosthetic valve thrombosis: An observation from Eastern India

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ABSTRACT

Introduction: Prosthetic valve thrombosis (PVT) is a life-threatening emergency. Thrombolytic therapy is emerging as a potential substitute. The objective of this study was to assess the safety and efficacy of Tenecteplase (TNK) in comparison to streptokinase (STK) in patients with PVT.

Materials and Methods: In this prospective study, patients with PVT who were not subjected to the surgery underwent thrombolysis with TNK (TNK arm) or STK (STK arm). Efficacy and safety of both treatment arms were judged from clinical, echocardiographic (ECHO), and Cinefluoroscopic parameters. Treatment outcomes and complications were compared between the two arms.

Results: Between December 2017 and December 2019, a total of 41 cases of PVT were enrolled to receive either TNK (n=23) or STK (n=18). After thrombolysis, complete recovery was significant in the TNK arm (82.6% [19/23] vs. 44.4% [8/18], respectively; p=0.007) irrespective of the valve position. This trend was observed in both mitral PVT (85.7% vs. 46.6%, respectively; p=0.03) and aortic PVT (77.8% vs. 33.3%, respectively; p=0.151). No failure was seen in the TNK arm but failure was observed in 1/3rd cases in the STK arm. No major bleeding was observed with either treatment. Minor bleeding and systemic embolization were non-significant (P=0.514). There were no deaths in the TNK arm but two patients (11%) from the STK arm died.

Conclusion: To our knowledge, this is the largest published comparative evidence indicating superior efficacy and equal safety of tenecteplase compared to streptokinase for the treatment of prosthetic valve thrombosis irrespective of valve position and NYHA class.

1. Introduction

Prosthetic valve thrombosis (PVT) is a life-threatening emergency. Clinical deterioration is imminent unless dealt with promptly and appropriately. PVT incidence varies from 0.5% to 8% per patient-year in the left-sided prosthetic valve and is up to 20% in the tricuspid position. In developing countries, the incidence is much higher and may even be up to 10% per patient-year.[1,2] Even though PVT is associated with increased morbidity and mortality,[3–7] its therapy is not standardized. Guidelines lack class I recommendations for any treatments of PVT due to the lack of randomized controlled trials (RCT). European Society of Cardiology (ESC) guidelines recommended surgery for all irrespective of clinical status. The Society of Heart Valve Disease recommends thrombolytic therapy (TLT) for all patients without contraindications. In developing countries like India, because of the unavailability of emergency surgery widely and the association of high surgical mortality rate of 5% to 20% from thrombectomy or re-do valve

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replacement,[8–10] the thrombolytic therapy (TLT) is an attractive first option. TLT has a higher success rate (75% - 83%) with a lower rate of complications. Further, the use of thrombolytics does not preclude the option for surgery in the event of failure. Various thrombolytic agents like streptokinase (STK), urokinase (UK), and recombinant tissue plasminogen activator (RTPA) have been used for nearly 12 to 24 hours with variable success rates. In patients with PVT, the success rate of STK is variable (64% to 90%) as compared to urokinase and alteplase.[11,12] There are no comparative studies so far assessing the efficacy and/or safety of one therapy over the other.

Evidence with tenecteplase (TNK) a synthetic tissue plasminogen activator (PAI), in the management of PVT, is limited. TNK has high fibrin specificity, increased resistance to plasminogen activator inhibitor-1 (PAI-1), longer half-life and can be given as a single intravenous (IV) bolus injection.[13] In a published case of PVT, TNK showed equivalent efficacy and lower risk of systemic bleeding among high-risk patients as compared to alteplase.[14] Given the lack of comparative studies from India assessing the safety and efficacy of TNK in comparison to the commonly used STK in the management of PVT, we conducted this study. The specific objectives of the study are the comparison of treatment outcomes and complications between the two treatments.

2. Materials and Methods

We conducted this prospective, observational study at a tertiary care center in Eastern India. All the patients diagnosed with PVT who were not willing to undergo emergency valve surgery and who were scheduled for thrombolysis were included in the study after approval of the Institutional ethics committee. Patients with any contraindication to thrombolysis were excluded. PVT was diagnosed using a combination of clinical, ECHO, and CF features. Clinical features included shortness of breath (NYHA Class II-IV), heart failure, absent or diminished prosthetic valve sound; features on transthoracic ECHO (TTE) were thrombus in the prosthetic valve, lack of disc mobility, increased transvalvular gradient (TVG), and increased pulmonary artery (PA) pressure, and observation of complete or partial loss of single or double leaflet motions with Cinefluroscopy (CF).

After taking informed consent, baseline clinical evaluation, all patients were subjected to TTE examination. Valve morphology, chamber enlargement, LV function, thrombus, mobility of disc, TVG, pulmonary artery hypertension (PAH), and Cinefluroscopy were observed. For mitral prosthesis, a Doppler-derived gradient of more than twice that of empirically observed in a normal prosthesis was considered prosthetic valve malfunction. Mean TVG of more than 6mmHg indicated PVT. For aortic prosthesis, a mean TVG of more than 40mmHg in absence of other causes was considered as PVT. Repeat ECHO was undertaken within 6 hrs, 12 hrs, and 24 hrs of thrombolytic infusion to assess the success of thrombolytic therapy. Trans-esophageal echocardiography (TEE) was used in selected cases wherein the diagnosis of PVT could not be confirmed or where LA thrombus was suspected in TTE.

2.1. Treatment allocation

All eligible PVT patients were subjected to thrombolytic therapy to receive either tenecteplase (TNK) and streptokinase (STK). TNK was administered as a single IV bolus in the dose of 1mg/kg within 10 seconds. STK was administered as 2.5 lacs units loading IV over 30 minutes followed by 1 lac/hour IV maintained for 24 hrs. Following thrombolysis, injection enoxaparin 60mg subcutaneously twice daily given for 5 days with 3 days of overlapping oral anticoagulant (warfarin or acenocoumarin) that was continued depending upon the desired INR value.

2.2. Efficacy evaluation

Efficacy was judged by the clinical and hemodynamic response from TTE and CF. Complete recovery was defined as clinical and hemodynamic improvement along with normalization or 50% reduction of TVG and restoration of valve mobility on TTE and CF. Partial recovery was considered when a significant symptomatic improvement with less than 50% reduction of TVG with partial recovery of disc or leaflets motion on TTE and CF. Clinical failure was defined as no clinical or TVG reduction improvement within 24 hours which included death or complication like major bleeding or systemic embolization requiring termination of therapy. Patients who had partial or no response underwent surgery after due informed consent.

2.3. Statistical analysis

Data were analyzed using statistical software IBM SPSS Statistics 24.0, SPSS South Asia Pvt. Ltd. The categorical variables were presented as frequency and percentages. Statistical differences for categorical variables were studied using the Chi-square test. For continuous variables, data presented with means for data which showed normal distribution and compared between the two treatment arms by independent sample 't's test. Distribution of pre-and-post thrombolysis in PVT of different continuous variables was compared within two treatment arms through the computation of median and interquartile range (IQR) and significance was assessed with the non-parametric Wilcoxon Test. P-value <0.05 was considered significant for statistical comparisons.

3. Result

Between December 2017 and December 2019, a total of 41 cases of PVT were enrolled. Out of 41 cases of PVT, 26(63.4%) was MVR, 9(22%) AVR, 6(14.6%) DVR. Patients were allocated to two thrombolytic treatment arms i.e., TNK arm (n=23) and STK (n=18). The mean age of cases was 36.7+7.6 years and the proportion of males was higher than females (78% vs. 22%, respectively). Rheumatic heart disease (RHD) affected 36 (87.8%) patients. The bicuspid aortic valve and the degenerative valve were observed in three (7.3%) and two (4.9%) patients. Mitral valves were affected in 29 (70.7%) patients. Among them, MVR and DVR were seen in 26 and 3 patients respectively. In mitral valve disease patients, 14 (48.2%) patients received TNK and15 (51.8%) patients received STK. Aortic valves were affected in 12 (29.3%) patients. Among them, AVR, and DVR were seen in 9 and 3 patients respectively.9 (75%) patients received TNK and 3 (25%) patients received STK (Table 1). The majority of the baseline characteristics like age, weight, previous disease, valve affected in PVT, valve age, Rhythm, presenting symptoms, LV dysfunction, symptom duration, INR value did not have a significant difference between the two groups (p> 0.05) (Table 1).

All patients presented with shortness of breath with varying degrees of NYHA Class II-IV. Palpitation (n=9, 22%) was second most common presentation followed by hemoptysis (n=7, 17%), hypotension (n=5, 12.2%).However, pre-syncope/dizziness (n=8 19.5%) was predominantly observed in aortic valve thrombosis. The average duration of presenting symptoms was 8.2 days. Atrial fibrillation (AF) was observed in 22 (53.7%) and LV dysfunction in 11 (26.8%) patients. The mean interval between thrombotic episode and valve implantation (valve age) was 2.1 ± 0.8 years. All patients (100%) did not have adequate anticoagulation. The mean INR value was 1.6 ± 0.4. In the TNK arm, there were two cases of repeat PVT which were treated with STK in the past (Table 1). The majority of mechanical prostheses were tilting disc (TTK Chittra) (21, 51.2%) followed by bileaflet Medtronic (11 26.8%) and St. Jude valves (9 29.9%) (Table 2).

Among the two arms, irrespective of the valve position complete recovery rate was statistically significant in the TNK arm than the STK arm (82.6% vs. 44.4%, respectively; P=0.007). This trend was observed in both mitral valve PVT (85.7 % vs., 46.7%, p = 0.039) and aortic valve PVT (77.8% vs. 33.3%, p= 0.151). There was no failure in the TNK arm but it was observed in one-third of patients in the STK arm, irrespective of valve involvement (Table 3).

Following thrombolysis, the median reduction in TVG in patients with mitral PVT was significant in the TNK arm (from 19.5 [IQR 17.5 - 22.5] mmHg to 5.5 [IQR 4 - 8.3] mmHg, P=0001) and STK arm (from 20 [IQR 18 - 22] mmHg to 10 [IQR 6 – 18] mmHg, P=0.008). In aortic PVT, median TVG reduction was significant in the TNK arm (from 50 (IQR: 48 – 57) mmHg to 20 (IQR: 18 – 31) mmHg, p=0.008). Also, the median reduction of peak TVG was significant in the TNK arm (from 66 [IQR: 63 – 80] mmHg. to 34 [IQR: 30 – 42] mmHgp=0.008).In the STK arm, reduction in the median TVG (from 52 to 36 mmHg) and peak TVG (from 64 to 48 mmHg) but was statistically non-significant (p= 0.109) (Table 4).

In complete recovery, TNK had a highly significant reduction TVG in both TNK (p=0.002) and STK (p=0.017) arms in patients with mitral PVT. In aortic Valve PVT, TVG and peak TVG showed a significant reduction in the TNK arm (p= 0.018 for both TVG and peak TVG). In the STK arm, there was only one patient with aortic PVT where in there was a reduction in TVG and peak TVG (Table 5).

However, in the partial/failed group, reduction inTVG was non-significant on either valve position between two treatment arms (Table 6). Left atrial clots of different sizes were observed in three patients of TNK and four patients of STK. Following either treatment, clots resolved among complete recovery patients whereas persisted in partial/failed group.

Overall, there were no complications in 20 (48.8%) patients. However, complete recovery without any complications was significantly more in the TNK arm compared to the STK arm (56.5% vs. 38.9%). There were 10 (24.4%) cases of minor bleeding, 4 (9.8%) cases of cerebral embolism in the form of TIA & stroke (Ischemic), 4 (9.8%) cases of peripheral embolism, 1 case (2.4%) of RCA embolism and 2 cases (4.9%) of death. The proportion of minor bleeding, cerebral embolism, peripheral embolism was lower in the TNK arm. There were two deaths in the STK group. However, the association of complications was found to be non-significant (p= 0.514). (Table 7).

4. Discussion

We report here a single-center tertiary care hospital study of 41 cases of PVT of mechanical valves treated with thrombolytics over 2 years. Management of PVT remains controversial. There are currently no randomized controlled trials favoring surgery over thrombolysis and vice-versa. To our knowledge, this is the first and largest comparative study, to date regarding the safety and efficacy of TNK in relation to STK for the treatment of PVT. In the present study, we had used CF and TTE for diagnosis and assessment of therapy in case of PVT as the sensitivity, specificity and positive predictive value of the test were 87%, 78%, 80% and 75%, 64%, 57% respectively as in Montorsi et al.[15]

Similar to previous reports, the single most important cause of thrombosis in our cases was the interrupted use of oral anticoagulants seen in all patients.[16] Our average duration presentation was early i.e., 8.2 days, which could be due to more association of risk factors like LV dysfunction in one-third of patients and AF in more than

Table 1: Baseline clinical profiles of two treatment arms

Parameters	Total (n=41)	TNK (n=23)	STK (n=18)	P-value
Age in year	36.7±7.6	37.9±8.6	35±6.1	0.135
		Gender		
Male	32 (78.0)	21 (91.3)	11 (61.1)	0.020
Female	9 (22.0)	2 (8.7)	7 (38.9)	
Weight in Kg	53.8±5.3	54.7±5.6	52.6±4.9	0.220
		Previous Disease		
RHD	36 (87.8)	22 (95.7)	14 (77.8)	0.121
BAV	3 (7.3)	0	3 (16.7)	
Degenerative	2 (4.9)	1 (4.3)	1 (5.6)	
		P/H surgery		
MVR	26 (63.4)	11 (47.8)	15 (83.3)	0.045
DVR	6 (14.6)	4 (17.4)	2 (11.1)	
AVR	9 (22)	8 (34.8)	1 (5.6)	
		Valve affected in PVT		
MV (MVR=26, DVR=3)	29 (70.7)	14 (60.9)	15 (83.3)	0.117
AV (AVR=9 DVR=9)	12 (29.3)	9 (39.1)	3 (16.7)	
Valve Age in year	2.1±0.8	2.0±1.0	2.1±0.5	0.850
		Rhythm		
NSR	19 (46.3)	9 (39.1)	10 (55.6)	0.295
AF	22 (53.7)	14 (60.9)	8 (44.4)	
		H/O PVT		
Yes	2 (4.9)	2 (8.7)	0	0.200
No	39 (95.1)	21 (91.3)	18 (100)	
		Presenting symptoms		
NYHA CL-II/III / IV	41 (100)	23(100)	18(100)	1.000
NYHA CL-IV	10 (24.4)	6(26.1)	4(22.2)	0.775
Hypotension	5 (12.2)	3(13.0)	2(11.1)	0.851
Dizziness / Ppresyncope	8 (19.5)	6(26.1)	2(11.1)	0.083
Haemoptysis	7 (17.1)	3(13.0)	4(22.2)	0.438
Palpitation	9 (22.0)	4(17.4)	5(27.8)	0.425
LV Dysfunction	11 (26.8)	7(30.4)	4(22.2)	0.556
Symptom Duration (Days)	8.2±3.5	8.5±3.8	7.8±3.1	0.568
Interrupted/Inadequate anti-coagulant	41 (100)	23 (100)	18 (100)	1.000
INR Value	1.6±0.4	1.6±0.4	1.6±0.4	0.812

Data presented as frequency (%) or mean ± standard deviation
RHD: Rheumatic Heart Disease, BAV: Bicuspid Aortic Valve, MVR: Mitral Valve Replacement, AVR: Aortic Valve Replacement, DVR: Double Valve Replacement, NSR: Normal Sinus Rhythm, AF: Atrial Fibrillation.

Table 2: Types of Mechanical valve prosthesis

Mechanical Prosthesis	Total (n=47)	Mitral (n=32)MVR (n=26) + DVR (n=6)	Aortic (n=15) AVR (n=9) + DVR (n=6)
Tilting disc (TTK Chittra)	23 (48.9%)	16 (50%)	8 (53.3%)
Bileaflet (St. Jude)	11 (23.4%)	6 (18.7%)	5 (33.3%)
Bileaflet (Medtronic)	12 (25.5%)	10 (31.2%)	2 (13.3%)

Table 3: Treatment outcomes between two arms

Outcome	Total (n=41)	TNK arm (n=23)	STK arm (n=18)	P value
Overall (n=41)				
Complete recovery	27 (65.9)	19 (82.6)	8 (44.4)	
Partial recovery	8 (19.5)	4 (17.4)	4 (22.2)	0.007
Failed	6 (14.6)	0	6 (33.3)	
Mitral Valve (n=29)				
Complete recovery	19 (65.5)	12 (85.7)	7 (46.7)	
Partial recovery	5 (17.2)	2 (14.3)	3 (20.0)	0.039
Failed	5 (17.2)	0	5 (33.3)	
Aortic Valve (n=12)				
Complete recovery	8 (66.7)	7 (77.8)	1 (33.3)	
Partial recovery	3 (25.0)	2 (22.2)	1 (33.3)	0.151
Failed	1 (8.3)	0	1 (33.3)	

Data presented as frequency (%)

Table 4: Comparison of TVG and PASP before and after two treatments

Parameters		Mitral valve (n=29)		Aortic valve (n=12)	
		TNK arm (n=14)	STK arm (n=15)	TNK arm (n=9)	STK arm (n=3)
Median TVG (mmHg)	Pre-TT	19.5 (17.5, 22.5)	20 (18, 22)	50 (48, 57)	52
	Post-TT	5.5 (4, 8.3)	10 (6, 18)	20 (18, 31)	36
	P-value	0.001	0.008	0.008	0.109
Peak TVG (mmHg)	Pre-TT	-	-	66 (63, 80)	64
	Post-TT	-	-	34 (30, 42)	48
	P-value	-	-	0.008	0.109
PASP (mmHg)	Pre-TT	62 (57.5, 76.5)	58 (52, 64)	46 (33, 63)	50
	Post-TT	35 (29.5, 42.5)	46 (30, 60)	30 (19, 34)	36
	P-value	0.001	0.011	0.012	0.593

Data presented as median (Interquartile range) PASP: Pulmonary Artery Systolic Pressure, TT: Thrombolytic Therapy.

Table 5: Comparison of TVG and PASP before and after two treatments among complete recovery patients

Parameters		Mitral valve (n=19)		Aortic valve (n=8)	
		TNK arm (n=12)	STK arm (n=7)	TNK arm (n=7)	STK arm (n=1)
TVG (mmHg)	Pre-TT	19.5 (16.5, 22)	20 (18, 23)	50 (48, 56)	52
	Post-TT	5 (4, 6.8)	6 (5, 8)	20 (18, 22)	20
	P value	0.002	0.017	0.018	-
Peak TVG (mmHg)	Pre-TT	-	-	72 (64, 84)	64
	Post-TT	-	-	30 (30, 34)	34
	P-value	-	-	0.018	-
PASP (mmHg)	Pre-TT	63 (58.5, 77.5)	58 (54, 72)	46 (32, 62)	52
	Post-TT	33 (28.5, 39.5)	30 (30, 38)	30 (18, 32)	36
	P value	0.002	0.018	0.018	-

Data presented as median (Interquartile range)

Table 6: Comparison of TVG and PASP before and after two treatments in partial recovery or failed patient group

Parameters		Mitral valve (n=10)		Aortic valve(n=4)	
		TNK arm (n=2)	STK arm (n=8)	TNK arm (n=2)	STK arm (n=2)
TVG (mmHg)	Pre-TT	22	19 (16, 21.5)	54	47
	Post-TT	16	18 (12.8, 21.5)	44	43
	P-value	0.180	0.558	0.157	0.180
Peak TVG (mmHg)	Pre-TT	-	-	63	63
	Post-TT	-	-	49	54
	P-value	-	-	0.180	0.655
PASP (mmHg)	Pre-TT	59	56 (52, 61.5)	51	44
	Post-TT	57	58 (50, 61.5)	38	47
	P-value	0.655	0.647	0.317	0.180

Data presented as median (Interquartile range)

Table 7: Complication ofthrombolytic therapy

Complications	Total (n=41)	TNK (n=23)	STK (n=18)	'p' value
No Complication	20 (48.8)	13 (56.5)	7 (38.9)	
Any complication	21 (51.2)	10 (43.5)	11 (61.1)	
Minor bleeding	10 (24.4)	5(21.7)	5 (27.8)	
Cerebral embolism (TIA/Stroke)	4 (9.8)	2(8.7)	2 (11.1)	0.514
Peripheral embolism	4 (9.8)	2(8.7)	2 (11.1)	
RCA embolism (STEMI)	1 (2.4)	1(4.3)	0	
Death	2 (4.9)	0	2 (11.1)	

TIA: Transient Ischaemic Attack, RCA: Right coronary artery, STEMI: ST Elevated myocardial infarction

50% of patients along with interrupted or inadequate anti-coagulants in a setting of prosthetic valve obstruction.

Complete recovery of the clinical and hemodynamic parameters by TTE was significantly observed with the TNK arm (82.6% vs. 44.4%, P=0.007) irrespective of valve position. Partial recovery was non-significant on either arm i.e., 17.4% in TNK and 22.2% in the STK arm. There was no failure in the TNK group whereas failure was observed in one-third of patients in the STK arm on either valve position. Similar benefits of TNK with a 100% success rate were also seen in a study from Sharma et al.[17] In 10 cases of left-sided PVT treated with TNK, they reported a clinical recovery in all patients.

There are no clear guidelines on the dosage of TNK in PVT. The previous reports had utilized the dose of 30mg (0.5mg per kg as IV infusion)[18] and 40mg as IV bolus dose. In contrast, the dosage of TNK in our study was higher i.e. 1mg/kg bolus with a higher success rate of 82.6% without any major hemorrhagic complications could be attributable to higher fibrin specificity associated with TNK, as shown in previous case reports of Sharma et al.[17] and TROIAtrials.[19] TROIA trial was the largest cohort study of thrombolysis for PVT showed equivalent success rate different regimes i.e., rapid STK, slow STK, rapid full dose TPA, slow half dose TPA and very low dose slow TPA. Rapid and full dose regime resulted in the faster opening of the valve and resolution of obstruction but the complication rate was lowest in low dose TPA (25mg over 6 hrs). It explains the higher success rate of 82.6% with rapid recovery in a high dose of TNK in our study. This could be crucial in critically ill patients with higher NYHA class where the early resolution of obstruction could be lifesaving. In our study, 10 cases (25%) were critically ill presenting with NYHA class-IV. There was a rapid improvement of clinical and hemodynamic status with the restoration of valve function in all critically ill patients. Though low dose TPA has been successful in the TROIAtrial,[19] the NYHA class-IV patients were excluded from the study. Therefore, accelerated regimes (high and bolus dose) would be the better choice in higher NYHA class and critically ill patients.

Two deaths (11.1%) were observed in the STK arm are attributable to the primary failure of thrombolytic therapy in patients with mitral PVT. The cause of death included refractory heart failure in one patient and recurrent VT/VF following severe LV dysfunction in another patient. There were no major bleeding events in either arm. Minor bleeding and systemic embolization were non-significant on either arm. All minor complications along with inferior wall STEMI cases were recovered spontaneously within 24-48hours without any residual deficit indicating superior efficacy and safety profile of tenecteplase over streptokinase. LA clots were seen in 21% of patients with mitral PVT and were resolved in those who responded to thrombolytic therapy on either arm.

5. Conclusion

Our results suggest that tenecteplase can be used safely in patients with Prosthetic Valve Thrombosis (PVT) irrespective of valve position and NYHA class resulting in rapid restoration of valve function and clinical improvement as compared to the conventionally used streptokinase, besides ease of administration i.e., bolus vs prolonged infusion. However, a randomized, controlled clinical study using a larger patient population is needed to assess the efficacy in comparison to other thrombolytics and also to decide the optimal dose of tenecteplase.

6. Source of Funding

None.

7. Conflict of Interest

None.

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