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Research Brief

Clinical outcomes of patients with mitral prosthetic valve obstructive thrombosis treated with streptokinase or tenecteplase

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ABSTRACT

Agent of choice for thrombolytic therapy (TT) in prosthetic valve thrombosis (PVT) is unknown. 84 mitral obstructive-PVT episodes treated with TT (43: Tenecteplase; 41: Streptokinase) were included in this prospective study. The incidence of primary end-point (CCS: complete clinical success, defined as complete or partial hemodynamic success with no complications or surgery) was 84.5% with recurrent PVT as a sole predictor. Bleeding and embolic manifestations were noted in 8.3% and 4.7% of episodes respectively. Tenecteplase use was associated with lower complication rate and a mitral EOA of <0.74 cm^2 at presentation predicts the need for extended thrombolysis (accuracy, 78.6%).

1. Introduction

Surgical valve replacement is currently the standard of care for the treatment of valvular heart disease. Prosthetic valve thrombosis (PVT) is a life-threatening complication with an average incidence of 1.8%–5.7% per patient-year.[1,2] Latest guidelines had recommended treatment with either slow-infusion low-dose thrombolytic therapy (TT) or emergency surgery in patients with a left-sided mechanical obstructive (O)-PVT.[3] Streptokinase (STK) and Urokinase are the only FDA approved agents for this purpose. However, many studies have shown that Tenecteplase (TNT) can also be used successfully by infusion[4] as well as bolus[5] for O-PVT.

2. Methods

This was a single centre, prospective cohort study that was conducted after IEC approval. Mitral O-PVT was diagnosed by echocardiography[6] and/or fluoroscopy.[7] Trans-esophageal Echocardiography (TEE) was used only in selective cases where the diagnosis could not be confirmed on 2D trans-thoracic echocardiography (TTE).

TTE Imaging was also carried out every 6 h and before changing treatment decisions. Patients are excluded, if they have contraindications to TT, severe ventricular dysfunction (LVEF <30%), severe unrepaired primary valvular pathology, associated with aortic or right sided O-PVT.

2.1. Systemic thrombolysis

Patients were thrombolysed with either TNT ([0.50 mg/kg]/24 per hour) or STK (30-min loading dose of 1,50,000–2,50,000 U, followed by 1,00,000 U/h) intravenous infusion. Choice of agent was based on the drug availability and at the discretion of treating

Abbreviations: TT, thrombolytic therapy; **STK**, Streptokinase; **TNT**, Tenecteplase; **EOA**, effective orifice area; **ET**, Extended thrombolysis; **O-PVT**, obstructive prosthetic valve thrombosis; **TVG**, Transvalvular gradient; **PHT**, pressure half time.

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physician. In any event of major thromboembolic or bleeding episode, TT is stopped.

Patients who had complete hemodynamic response at any point during therapy or partial hemodynamic response even at the end of 48 h infusion, TT was stopped and were further managed with heparin. Patients with persistent hemodynamic instability were treated surgically.

2.2. Adjuvant care

Heparin was withheld during TT. Heparin (UFH) was infused at a rate of 1000 U/h (adjusted to maintain aPTT at 2.0–2.5 times the normal) for 48 h and later Inj. enoxaparin was administered at a dose of 1 mg/kg/SC twice daily. Overlapping acenocoumarol was started and dosage was adjusted until INR fell in range of 2.5–3.5.

During in-hospital course patients were managed with diuretics, inotropes, vasopressors, ventilator (invasive/non-invasive) support were ever felt appropriate by the treating physician.

2.3. Outcomes measures

Composite of hemodynamic success (HS),[8,9] embolic and bleeding manifestations were used to define clinical success (CS). Complete CS was defined as complete or partial HS with no surgery and/or bleeding and/or embolic features. Clinical failure was defined as death (due to any cause) and/or hemodynamic failure. Incidence of complete CS was the primary end-point and secondary end-points were the incidence of composite adverse events (death or surgery or embolic or bleeding episodes), duration of TT and duration of the hemodynamic support.

2.4. Statistical analysis

Continuous and categorical variables were reported as mean- and number of observations (n), respectively. Multivariate regression analysis was performed to determine the predictors of in-hospital outcomes. Area under receiver operator characteristic (AUROC) curves were analysed for an optimal cut-off. A $p < 0.05$ was considered significant statistically. All the statistical analyses were performed using EZR® (3.5.2. R foundation).

3. Results

A total of 84 eligible mitral O-PVT episodes (15 recurrent) were included (62%, females) and all are breathless at presentation. Absence of therapeutic anticoagulation was the main risk factor. Mean mitral trans-valvular gradient (TVG) and effective orifice-area (EOA) were 25.5 ± 4.5 mmHg and 0.91 ± 0.27 cm^2 respectively. 41 episodes were treated with STK.

Complete HS and CS were achieved in 81% and 84.5% of episodes respectively. 2 patients needed surgery and 2 other patients died. Incidences of bleeding and embolic manifestations were 8.3% and 4.7% respectively. Mean duration of TT was 25.6 h (extended thrombolysis, ET in 16 episodes) and hemodynamic support was needed in 24 episodes (mean: 7.1 h), Table 1. In multivariate analysis, recurrent O-PVT was associated lower complete CS. Mitral EOA at presentation and TNT use were associated with duration of TT and hemodynamic support respectively. TNT was associated significantly lower composite adverse event rate, Table 2. A mitral EOA of <0.74 (AUROC: 0.74) predicts the need for ET with an accuracy of 78.6% (sensitivity and specificity of 75% and 79.4% respectively). Supplementary Figure 1.

4. Discussion

Younger age, female predominance and sub-therapeutic INR in majority of O-PVT was seen; an epidemiology consistently demonstrated in studies from developing countries.[10] We did not used TEE to quantify thrombus because, a sizeable proportion of study patients were not stable enough to perform a safe TEE at presentation. Recurrent PVT was associated with significantly lower success. Similar poor performance was published, where following TT, <50% of patients had complete gradient recovery with >1/3rd patients experiencing death.[11] Lower mitral EOA may represent the higher thrombotic burden on leaflets and thus been associated with longer duration of TT. 4 systematic reviews on TT for PVT showed a complete success rate of about 70%–80%.[12–15] However, success might depend upon the valve position, definition of 'success' used, size of obstructing thrombus, previous co-morbidities, nature of systemic TT used (76.6% with STK and 90% with TNT),. Among STK treated patients, 2 experienced major bleeding (massive hematemesis and other hemorrhagic stroke) and 1 had embolic stroke. There were no major bleeding episodes with

Table 1
Clinical presentation data, management and study outcomes.

Variable		Variable	
Age (years)	41.1 ± 6.1	STK treated	41 (48.8%)
Female	52 (61.9%)	Extended thrombolysis	16 (19%)
tilting disc	59 (70.2%)	Hemodynamic support	24 (28.5%)
SH duration (days)	6 ± 3.8	LVEF (%)	57 ± 4.9
Recurrent	15 (17.8%)	mitral EOA (cm^2)	0.9 ± 0.27
NYHA III	72 (85.7%)	Trans-mitral gradient (mmHg)	25.5 ± 4.5
On aspirin prophylaxis	16 (19%)	**Clinical events with TT**	
On Penicillin prophylaxis	44 (52.4%)	Bleeding	7 (8.3%)
Duration since surgery	5.62 ± 3.7	Embolic manifestations	5 (5.9%)
INR	1.4 ± 2.8	death*	2 (2.4%)
Platelet count (10^4/dl)	23 ± 4.9	surgery*	2 (2.4%)

* SH: symptom onset to hospital presentation, STK: streptokinase. EOA: effective orifice area, LVEF: left ventricular ejection fraction, Bleed: as per ISTH criteria. *thrombolytic failure = 4 (4.8%). Surgery: both were STK pre treated - discharged uneventfully. TT: Thrombolytic therapy. Bleeding: 3 - gum bleeding (2: STK), 1 - hematuria (STK), 1 - surgical site bleeding (TNT) and 2 had major bleeding. Embolic: 3 patients had peripheral embolism (2: STK) and another 2 patents had stroke.

Table 2
Incidence and Predictors of study outcomes*.

Outcomes				
primary outcome	N (%)	Secondary outcomes		
Composite clinical success	**71 (84.5%)**	**Composite adverse events (N, %)** **Duration of TT (hours)** **Duration of hemodynamic support (hours)**		**13 (15.4%)** 25.6 ± 5.6 7.1 ± 3.5
Predictors of in-hospital outcome **Complete Clinical success: Univariate logistic regression**				
	β	**OR**	**95% CI**	**p**
Recurrent PVT	1.31	2.88	1.66–3.12	**0.03**
TNT (yes = 1)	1.14	3.14	0.89–10.99	0.08
EOA	1.17	3.22	0.40–25.9	0.27
SH interval	0.12	1.13	0.87–1.46	0.34
TT duration	0.09	1.19	0.78–1.66	0.24
Composite adverse events: Univariate logistic regression				
	β	**OR**	**95% CI**	**p**
TNT (yes = 1)	−1.45	0.23	0.05–0.91	**0.03**
TT duration	0.44	1.44	0.72–2.12	0.19
Aspirin (yes = 1)	−0.30	0.74	0.14–3.72	0.71
Thrombolytic therapy duration: Univariate linear regression				
	β	**SE**	**t**	**p**
Mitral EOA	−8.54	3.43	−2.49	**0.01**
TNT	−3.24	1.39	−1.66	0.07
Hemodynamic support duration: Multivariate linear regression				
	β	**SE**	**t**	**p**
Mitral EOA	−4.66	2.13	−1.78	0.09
TNT	−4.17	1.12	−2.11	**0.02**

^ Variables assessed are: Age; sex; Aspirin use; recurrent PVT; tilting disc; SH interval; TNT use; mitral TVG; mitral EOA; LVEF and TT duration (only relevant variables and significant in univariate analysis were presented). TT: thrombolytic therapy; EOA: effective orifice area; TVG: transvalvular gradient; TNT: Tenecteplase; SH: symptom onset to hospital, PVT: prosthetic valve thrombosis.
bold: statistically significant.
*: provided at the foot notes of table

TNT, but its use resulted in TIA in one patient. With STK, studies had documented an average bleeding and embolism rate of 8.5% and 6.5% respectively (6% each with TNT), Supplementary Table 1. Non-utilization of TEE for evaluating the thrombus burden and single centre nature with small sample were notable limitations.

5. Conclusion

In left sided O-PVT systemic thrombolytic therapy (with streptokinase or tenecteplase) is associated with <5% failure rate. Recurrent PVT being associated with lower complete clinical success, thus patient education for proper drug compliance and follow-up is imperative. Compared to STK, TNT infusion is associated with statistically better safety profile and faster recovery, thus should be preferred. Lower mitral EOA (<0.74 cm^2) at presentation predicts the need for extended thrombolysis with good accuracy (around 78%).

Declaration of competing interest

All authors have none to declare.

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None.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ihj.2021.02.005.

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