Management and Clinical Outcomes in Patients with Mechanical Tricuspid Valve Thrombosis

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Abstract

Background: The incidence of prosthetic tricuspid valve (TV) thrombosis is the highest among heart valves. It can lead to high morbidity and mortality without proper treatment. In this study we sought to report the management and clinical outcomes of patients with mechanical TV thrombosis. Methods: In in a retrospective single-center study, all patients with mechanical TV thrombosis were evaluated from 2006 to 2017. The data on baseline characteristics, management of mechanical TV thrombosis, and the rates of adverse events during follow-up period were assessed. Results: A total of 67 episodes of mechanical TV thrombosis in 42 patients were observed. The mean age of patients was 45.5±14.3 years (19 to 77), and overall two-thirds were female. Thrombolytic therapy (TT) was used in 41 (61.1%), anticoagulant intensification in 15 (22.3%), and surgery as first approach in 11 (16.4%) episodes; subsequently, surgery as the final approach was implemented in 20 (29.8%) episodes. There were a total of 2 (2.98%) in-hospital deaths. Moreover, 2 (4.87%) episodes of retroperitoneal hematoma and 1(2.43%) episode of non-hemorrhagic thalamic infarct in TT group, and 1 (5%) episode of non-hemorrhagic stroke following surgery were developed. The rates of freedom from recurrent thrombosis were 84%, 61%, and 21% at the end of 2, 4, and 10 years, respectively. Survival rates and freedom from chronic valve dysfunction was 93%, 82%, and 75% after 1, 4, and 10 years. Conclusions: The recurrent thrombosis requiring intervention is a major complication of mechanical TV, which underscores individual-approached therapy and close follow-up to improve outcome.

1- Introduction

Tricuspid valve (TV) prosthesis is associated with an 11.7 times higher risk of thrombosis than other heart valves and it may occur in approximately 20% during the first postoperative year [1,2]. In non-randomized cohorts of thrombosed mechanical or biological TV prostheses, fibrinolysis has been successful to normalize hemodynamics; therefore, AHA/ACC and ESC/EACTS recommend that fibrinolysis is reasonable in patients with TV thrombosis [3,4]. Thrombolytic therapy has been successfully used as a first management in obstructive right-sided valvular thrombosis [1,3]. Moreover, several regimens of thrombolytic agents, including high dose recombinant tissue plasminogen activators or streptokinase, a low dose-slow and even ultraslow infusion of tissue plasminogen activators, and direct intra-atrial infusion of thrombolytic has been attempted [5-8]. However, there is limited data on optimum choice of treatment.

As the mechanical TV replacement is rarely performed, there is lack of data about the outcomes in large series, so the recommendations of guidelines are based on small case series and case reports. In a review study, Huang et al. [9] reported the clinical outcomes of forty-eight patients with mechanical TV thrombosis in the literatures from 1995 to 2013 year that underwent thrombolytic therapy and/or surgery. They found

that complete success with thrombolytic therapy developed in 88% with no serious complications; however, the late outcomes of patients were not completely described.

In this single-center study, we sought to conduct a comprehensive retrospective study to evaluate the management and the early outcomes of patients with mechanical TV thrombosis, and also to provide long-term follow-up.

2- Materials and Methods

2-1 Study population

In this retrospective study, all patients admitted with mechanical TV dysfunction in our center from February 2006 through December 2017 were identified and reviewed in a single-center manner in Tehran, Iran. The informed consent was not obtained from patients, and the study protocol was approved by the local ethics committee of our institution. Any episode of mechanical TV thrombosis was enrolled into the study. The suspected cases of prosthetic valve infective endocarditis were excluded. If a patient was readmitted at a different time with recurrent TV thrombosis, it was considered as a recurrent event. All clinical and echocardiographic features were collected. Anticoagulation status at the time of admission and through six months before index event was recorded based on the amount of international normalized ratio (INR). The aims of study included (1) to evaluate the response to therapy in patients with mechanical TV thrombosis in different treatment groups and also to assess the adverse events during admission and follow-up period, (2) to identify how echocardiographic and fluoroscopic examinations could help as a diagnostic tool to guide therapy.

2-2 Echocardiographic and fluoroscopic evaluations

All patients underwent transthoracic echocardiography (TTE) and fluoroscopic examinations. The diagnosis of mechanical TV thrombosis was made based on clinical presentation, physical examinations, and imaging features on echocardiographic and/or fluoroscopic evaluations. The type of mechanical TV thrombosis was considered obstructive when a high trans-prosthetic pressure gradient was observed on TTE and reduced or fixed leaflet mobility was detected by fluoroscopy. The cutoff values for Doppler parameters were based on the latest recommendation. The TV peak velocity [?]1.9 m/s, the mean of trans-tricuspid pressure gradient [?]6 mm Hg, and the pressure half time [?]130 ms were suggestive of possible tricuspid prosthetic obstruction [2].

2-3 Therapeutic groups

The choice of treatment approach was based on the discretion of attending physicians. There were three therapeutic strategies, including thrombolytic therapy, anticoagulant intensification, and surgery. In thrombolytic group, the most common protocol included intravenous streptokinase with a loading dose of 250,000 IU in 30 minutes followed by 100,000 IU per hour for 24-72 hours, intravenous reteplase with a bolus of 10 units over 2 minutes followed by a second dose of 10 units given after 30 minutes, and alteplase with a bolus of 10 mg in 1 minute plus 90 mg within 2-3 hours. The fibrinolytic agents initiated when the INR was $<$2.5. The heparin infusion was started after fibrinolytic therapy as a 70 IU/kg bolus (maximum 5000 IU) and a 16 IU/kg per hour (up to 1000 IU/hour) to reach a target activated partial thromboplastin time (a-PTT) of 1.5-2 times of the average reference range, followed by warfarin with an overlap period of at least 5 days until desired INR maintained. The anticoagulant intensification group comprised of a high dose of unfractionated heparin to obtain 2-3 times of normal a-PTT and warfarin was also continued during this period. The surgical modality included re-replacement of prosthetic valve by a mechanical or biologic valve and/or thrombus/pannus excision.

2-4 Definitions for successful and failed therapies

Response to treatment was defined as the following criteria: (1) “successful” as normalization of increased trans-prosthetic gradient on echocardiographic examinations associated with a normal or an acceptable leaflet motion by fluoroscopy in the absence of major adverse events; (2) “partially successful” as a partial decrease

in gradients on echocardiography and a partial improvement in leaflet motion by fluoroscopy; (3) "ineffective" as no improvement in Doppler indices on echocardiography and leaflet mobility by fluoroscopy.

2-5 Follow-up outcomes

The follow-up of patients included in-hospital and after discharge outcomes. Major adverse events were defined as major nonfatal bleeding (i.e., intracranial hemorrhage, gastrointestinal bleeding, and retroperitoneal hemorrhage), thromboembolic events (i.e., pulmonary thromboembolism, stroke, limb ischemia, and acute coronary syndrome), and all-cause in-hospital mortality. All patients were also followed up by telephone interview and reviewing medical charts provided by patient and/or relatives/guardians. All-cause mortality, recurrent episodes, chronic valve dysfunction, and freedom from morbidities were recorded during follow-up period.

2-6 Statistical analysis

Descriptive statistics were reported as mean (± SD) or median (interquartile range) values for continuous variables, and as frequency (percentage) for the categorical variables. To compare continuous variables between two groups, the independent t-test or Mann-Whitney U test was used. The categorical variables were compared between groups using the chi-squared test. Friedman test was used to compare the distributions of 3 or more dependent variables. Multivariate analysis was conducted to identify the predictors of study endpoints by including significant covariates (i.e., age, sex, atrial fibrillation, admission INR, functional class, size of thrombus, elapsed time since valve surgery, redo-operation, recurrent episodes, and treatment types) into multiple logistic regression analyses. The survival plot and freedom from recurrence were estimated using the Kaplan-Meier method. The $p < 0.05$ was considered statistically significant. All statistical analyses were performed using the SPSS version 21 (IBM, Armonk, NY).

3- Results

3-1 Baseline characteristics

Sixty-seven episodes of mechanical TV thrombosis in forty-two patients were evaluated. The mean age was 45.5 ± 14.3 years (range 19-77) with a predominance of females (28 women, 66.6%). A total of 47 (70.1%) episodes were developed in females. The median frequency of TV thrombosis episodes in patients was 2 (1-3), and the median number of previous sternotomy was 2 (2-3). Twenty episodes (29.8%) occurred in [?]12 months and 31(46.2%) episodes in [?]24 months. All patients were on warfarin, and aspirin use was documented in 48 (71.6%). The history of obvious recent discontinuation of warfarin was identified in two patients due to minor medical interventions and in one patient because of trauma. The Ebstein's anomaly was the most common congenital heart disease observed in 5 (11.9%) patients with 8 (11.9%) episodes of thrombosis. Other baseline characteristics are summarized in

(Table 1).

3-2 Echocardiographic and fluoroscopic findings

Obstructive TV thrombosis were found in 65 (97%) based on both echocardiographic Doppler assessments and leaflet movement in fluoroscopy. Transesophageal echocardiography (TEE) was performed in 20 (29.8%) episodes. The reductions in the averages of mean gradients and pressure half-time were significantly different after successful treatment ($p < 0.001$). Transvalvular leak severity decreased after thrombolytic therapy, and its changes were statistically significant ($p = 0.013$). Decrease in mean inferior vena cava size and increase in its respiratory collapsibility after treatment were statistically significant ($p = 0.001$ and $p < 0.001$, respectively), revealing decreased RA pressure after treatment. There were no statistically significant changes in right ventricular (RV) function, RV peak systolic myocardial velocity (Sm), Tricuspid Annular Plane Systolic Excursion (TAPSE), and mean pulmonary artery pressure (mean PAP). First fluoroscopy on admission revealed both leaflets blockade in 30 (44.7%), one leaflet blockade in 28 (41.8%) and limitation of motion in 9 (13.4%). Of fixed occluders of TV leaflets, 71.6% were in semi-open position. All measured echocardiographic parameters before and after treatment were summarized in **(Table 2)** .

3-3 Treatment groups

Thrombolytic therapy was used in 41 (61.1%) episodes, intensification of anticoagulant in 15 (23.4%), and surgery was performed in 11 (16.4%) episodes as the first approach and finally in 20 (29.8%) episodes (8 patients underwent surgery following failed thrombolytic and 2 due to ineffective anticoagulant intensification therapy).

3-3-1 Thrombolytic therapy

Streptokinase in 15 (36.6%), reteplase in 10 (24.3%), and alteplase in 7 (17.1%) episodes were used as a single agent, and 9 (21.9%) episodes were given a combination of two fibrinolytic agents consecutively. Complete hemodynamic and clinical success in absence of major complication was achieved in 28 (68.2%), partial success in 4 (9.7%), and ineffective thrombolytic therapy in 9 (21.9%) episodes, respectively. One in-hospital death (2.43%) occurred in a 70-year-old man unresponsive to thrombolytic and medial therapy due to worsening of heart failure symptoms. Eight (19.5%) episodes, which had partial or ineffective response, underwent subsequent surgery. Among episodes given reteplase alone (n = 10) or in combination with another fibrinolytic (n = 5), the total success rate was 86.6% (all episodes which received reteplase alone were successful), but there was no statistically significant difference among thrombolytic agents in this regard. Concerning major bleeding complications, there were no intracranial hemorrhage and gastrointestinal bleeding (GIB) (3 patients with a history of GIB or with a suspected recent upper and lower GIB symptoms underwent direct surgery). Retroperitoneal hematoma was noted in 2 (4.87%) episodes; one occurred in a 62-year-old lady after receiving 625,000-unit streptokinase in 10 hours without a loading dose, manifested as mild pelvic hematoma associated with abdominal wall hematoma, which hindered continuation of thrombolytic therapy; another limited mild retroperitoneal hematoma was observed in a 51-year-old man with the repeat of a second dose of rapid infusion of Alteplase after 48 hours. Documented minor bleeding was reported in 11 (26.8%) episodes, including notable ecchymosis (n = 5), epistaxis (n = 3), hemoptysis (n = 2), and hematuria (n = 1). Concerning thromboembolic events, there was 1 (2.43%) non-hemorrhagic thalamic infarct in a 23-year-old lady with a history of mitral valve replacement, but no AF rhythm. The mean of hospital stay was 13.6 +- 10 days.

3-3-2 Anticoagulant intensification

Successful response to anticoagulant intensification was obtained in 3 (20%) episodes; two in non-obstructive and one in obstructive valve dysfunction, respectively. Partial response was observed in 8 (53.3%) episodes. Ineffective response was seen in 4 (26.6%), of which 2 underwent a subsequent surgery and the other two patients remained on anticoagulant and medical therapy. The mean of hospital stay was 12.5 +- 8 days.

3-3-3 Surgery

Surgical Procedures included valve replacement with either a new mechanical or a bioprosthetic valve (n = 18, 90%), and previous valve cleaning (n = 2, 10%). Organized thrombus or a combination of pannus and thrombus was reported in 5 (71%) episodes of failed thrombolytic therapy, while was noted in 4 (36.3%) episodes not receiving fibrinolytic (p = 0.03). Complete hemodynamic and clinical success was obtained in eighteen (90%). One death (5%) occurred after surgery in a 49-year-old man with a history of redo TV replacement and treated with a strategy of slow (6 hours), single infusion of low-dose alteplase (50 mg) before surgery, and one patient (5%) was complicated with non-hemorrhagic stroke following operation. The means of hospital stay among patients underwent surgical procedure as a first step and those after failed thrombolytic were 23.2 +- 19 and 24.5 +- 8.2 days, respectively.

3-4 Predictors of successful intervention

In those who had successful response to thrombolytic therapy, median (IQR) elapsed time from surgery was significantly less than those with partial or ineffective responses (p = 0.02), demonstrated in **(Fig. 1)** . With respect to admission INR and the average INR of prior 3-6 months, it was observed that patients with successful response had lower mean of admission INR than those with unsuccessful response (2.37 +- 1.23 vs. 2.98 +- 1.16), while the latter group with unsuccessful response had lower average INR in prior 3-6 months

(2.41 +- 0.36, p = 0.004). Although there was no statistically significant association between functional class and response to therapy, those who had successful response had less extremity edema (23.5%) and less increased jugular venous pressure (5.9%, p = 0.012).

3-5 Recurrent thrombosis

There were 24 episodes of recurrent mechanical TV dysfunction due to thrombosis. Of these episodes, 10 occurred following thrombolytic therapy, 8 after anticoagulant intensification, and 6 following surgical procedure. There was significantly shorter mean of interval between recurrent events and previous thrombolytic treatment than surgery (13.2 +- 14.1, 95% confidence interval [CI] 5.8-20.5 vs. 66 +- 36, 95% CI 36.8-95.1 months, p <0.001), in**) Table 3(** . With respect to the choice of treatment and response to therapy, in recurrent episodes following previous thrombolytic therapy, five (50%) cases received fibrinolytic again as the treatment option; of which three (60%) were successful and two (40%) cases required subsequent surgery due to failed thrombolytic treatment. In recurrent episodes following previous redo TV replacement, five (83.3%) cases received successful fibrinolytic therapy. Although, five (62%) episodes with partial response in our study were a recurrent episode, there was no statistically significant association regarding treatment response in recurrence and non-recurrence episodes (the thrombolytic success rate was 66.7% in episodes which were not a recurrence).

Sixteen (38%) patients presented with at least one episode of recurrent thrombosis during the median follow-up time of 31.1 months (0.53-155.9). Kaplan-Meier estimation for freedom from the first recurrence of thrombosis revealed that at the end of first 2 years irrespective of the treatment strategy, 84% of patients were free of recurrent thrombosis; however, this declined to 61% and 21% at the end of 4 and 10 years, respectively. The median time for the first recurrence in patients was 85.5 months (95% CI 41.8-129.2), **(Fig. 2).**

3-6 Predictors of mortality and morbidity

Follow-up after the last episode of valve thrombosis was available in 37 (92.5%) patients. During follow-up, 4 (10.8 %) patients died and 3 (8.1%) patients developed chronic valve dysfunction. Two deaths occurred in patients with post-redo TV replacement (one due to infective endocarditis and another in a patient with associated post-operative stroke and cancer); One death occurred following successful thrombolytic therapy (due to heart failure), and one patient died after unsuccessful anticoagulant intensification with a history of previous thrombolytic therapy and chronic valve dysfunction. The frequency of death and chronic valve dysfunction were 5% and 5% in thrombolytic therapy group, respectively, while these proportions were 25% and 50%, respectively, for anticoagulant intensification group. Moreover, mortality rate in surgical group was 15.3% during follow up.

Atrial fibrillation and RV dysfunction were significantly associated with death by univariate analysis (p = 0.02), though after the multivariate analysis adjusting for age, sex, redo-operation, recurrent episode, and treatment type the correlation was not statistically significant. Survival rate and freedom from chronic valve dysfunction in the first year was 93%, while it was 82% after 4 years. The 10-year survival rate and freedom from chronic valve dysfunction was estimated 75% by Kaplan-Meier curve. The median follow-up duration was 37.2 months (0.99-205.3), depicted in **(Fig. 3)** .

Discussion

The lower velocity of flow in the right heart and the commonly larger size of TV prosthesis, makes thrombus formation easier. Moreover, RV dysfunction, atrial fibrillation, right atrial enlargement, pulmonary arterial hypertension, hypercoagulable state, and multiple prostheses are other common predisposing factors; therefore, biological valves were assumed as the gold standard and mechanical valves as the challenging device in TV position [8,10-12]. However, mechanical valve has been used more frequently due to its presumed longer durability in the case of adequate anticoagulation maintenance, and higher risk for redo surgery in these patients, as they usually have a history of multiple sternotomies owing to previous TV repair, frequent other valve replacements, or congenital heart surgeries [13,14]. The present report is the largest and the

most comprehensive single-center study evaluating the isolated mechanical TV thrombosis with respect to treatment modalities and response to therapies during follow up period.

Our patients have encountered this serious and morbid condition after an average elapsed time from surgery of 49.9 (range 0.4-276) months, while 29.8% of episodes occurred in [?]12 and 46.2% in [?]24 months following surgical TV replacement. This is almost in agreement with previous studies evaluating the rate and prognosis of TV thrombosis. Roudaut et al. [11] described a median time from valve replacement to thrombosis of 4.3 years (14 days to 18 years) and an incidence rate of thrombosis in 24% of patients in the first postoperative year. In a meta-analysis by Liu et al. [10] valve thrombosis occurred at a mean follow-up of five to seven years and structural bioprosthetic degeneration occurred at an average of seven to nine years after TV replacement. These findings emphasize the importance of adequate anticoagulant treatment with a special consideration of postoperative period as well as during follow-up period.

The sub-therapeutic INR values less than 3 and 3.5 was seen in 70% and 82% of episodes at the time of admission, respectively. As it could not be the only clue to anticoagulation status, due to a probable more chronic process of a usually multilayered clot, we also assessed the average amount of previous 3-6 months. Contrary to left-sided valves, guidelines do not specify recommended levels of INR for mechanical prosthesis in TV position. It is advocated that target INR should be adjusted to patient risk factors and the thrombogenicity of the prosthesis (i.e., mitral or tricuspid position, atrial fibrillation, and a history of previous thromboembolism). In addition, a single INR target is mandatory for efficient antithrombotic therapy to identify that the acceptable range is 0.5 units of INR levels on each side, avoiding the upper or lower edge of the range values. We could not determine such a target due to our study type, but according to guidelines implications and considering the valve type in our study, we recommend the INR target of at least 3 for lower risk patients and 4 for higher risk ones with a history of previous thrombosis [3,4] Shapira et al. [15] recommended the target level of INR as 3.5-4 for patients with TV prostheses, and Zhang et al. [16] considered the target INR levels of 3-3.5. On the other hand, we should also take into account that patients may have lesser compliance with higher INR goals [17]. In addition, Aspirin 75 to 100 mg daily in combination with vitamin K antagonist anticoagulation in all patients, and the continuation of warfarin with a therapeutic INR levels in patients undergoing minor procedures is recommended to prevent the rapid decrease in the INR and the risk of thromboembolism [3,4].

Complete hemodynamic and clinical success rate of 68.2% following thrombolytic therapy was observed in this study. It is fairly within the ranges of previous similar studies [7,9,14,18,19]. It should be considered that different success rates may be possibly caused by different patient selection, diagnostic modalities, fibrinolytic regimens [20], and the definition of outcomes. Additionally, most of our cases (97%) were diagnosed as obstructive TV thrombosis, and we evaluated successful response in absence of important complications (such as retroperitoneal hematoma and stroke). There was no statistically significant difference regarding the success rate among thrombolytic treatment subgroups. This might be due to insufficient number of cases in certain subcategories [20].

Our study highlighted that thrombolytic response depends on the chronicity of thrombosis and the presence of pannus formation. We should bear in mind that valve thrombosis could be an acute, subacute or chronic event and thrombi are typically formed of different clot layers, with variable degrees of organization. This indicates that trying thrombolytic therapy as the first step treatment is sensible in most patients, even though probably with an incomplete resolution of clot [11,12]. In addition, regarding the treatment strategy in recurrent cases, it seems that the prior management of patients had a substantial impact on treatment choice by physicians. In those with a history of prior thrombolysis and anticoagulant intensification there were more trends towards surgery, while in patients with previous TV surgery, more patients were treated with fibrinolytic. In a former study in cases received fibrinolytic, it was revealed that the level of anti-tissue plasminogen activator antibodies (ATA) may increase during thrombolysis with rt-PA infusion and may interfere with the success rate, necessitating a higher dose for complete success and play a role in resistance to fibrinolysis [21].

Retroperitoneal hematoma may happen unexpectedly in patients under anticoagulant treatment. It may

be life-threatening and leads to abdominal compartment syndrome, requiring prompt surgical approach [22]. The lowest non-cerebral major bleeding was reported to be 1.7% by Ozkan et al. [23] with ultraslow thrombolytic therapy. Moreover, we found an embolic cerebrovascular event during thrombolytic therapy, in spite of being primarily unpredictable in right sided PVT fibrinolysis. Cerebral embolism following thrombolytic treatment have been reported to have an incidence of 3-10% and is even more frequent in the presence of atrial fibrillation [20]. This heighten the role of TEE in risk stratifying of patients for thrombolysis. Given the high rate of left-sided valve replacements, congenital heart disease and AF rhythm among TVR patients, they should be evaluated for the presence of thrombus formation on left-sided prosthetic valves, left atrium or its appendage, and probable PFO as the source of emboli, as well.

Moreover, despite the low rate of mortality and major non-fatal complications in the course of in-hospital management, there were considerable recurrent episodes throughout the entire follow-up period. Thirty-eight percent of our patients experienced at least one episode of recurrent TV thrombosis. Recurrence rates after thrombolytic therapy were reported from 11% to 32% in similar studies [18,21,24] and fibrinolysis was associated with a significantly higher rate of recurrence, though none of previous reports has described in isolated mechanical TV thrombosis [18] According to our findings, it seems that incomplete resolution of thrombosis and the presence of pannus are remarkable triggers for re-thrombosis. We should mention the "Doppler silent" phenomenon, which implies that complete or acceptable normalization of valve occluder movement on fluoroscopy and valve gradients on echocardiography may not be merely the conclusive signs of complete thrombus resolution, and further visualization by TEE seems to be essential [25] So, a considerable number of our patients might have needed the continuation of thrombolysis as TEE was not performed in a significant number of patients.

Finally, novel diagnostic and therapeutic approaches are still evolving. Sixty-four-slice multi-detector computed tomography proved to be helpful in identifying masses amenable to thrombolysis in patients with prosthetic valve dysfunction. A high attenuation suggests pannus overgrowth and is associated with reduced response to fibrinolysis, whereas a lower value is associated with thrombus formation [26]. With regard to treatment, catheter-directed thrombolysis in selected patients may render the potential advantage of local thrombolysis with a much lower dose than systemic therapy, possibly providing better efficacy while reducing the risk of bleeding complications [8,16,27]. The selection of type of prosthetic valve is another important issue, so that the availability of transcatheter valve-in-valve replacement can change the trade-offs between mechanical and bioprosthetic valves [3]. Tricuspid valve-in-valve procedure was shown to be technically feasible in a number of studies in patients with a wide range of valve size [13,28]. This will be more interesting when we consider the relatively short average time to thrombosis and a high recurrence rate in our study together with the data derived from former studies indicating mean reoperation time of 44.2 months for mechanical prosthesis [29].

Study limitations

This report suffers from some limitations. Firstly, this study was a retrospective study and the selection bias could not be avoided. Secondly, the TEE examination was not carried out in every patient and the thrombus size was not measured before and after treatment in all individuals. Thus, we did not consider the extent of reductions in thrombus diameter and/or area in defining response to therapy, though it was available in some patients. Thirdly, the heterogeneity of underlying valvular pathology existed, which can influence the outcomes of patients.

Conclusions

Recurrent valvular thrombosis is a significant morbid situation affecting a group of patients with mechanical valve in tricuspid position. Chronic thrombosis and the presence of pannus are associated with a diminished thrombolysis success. Inadequate use of fibrinolytic agents in terms of dose and time could result in an incomplete disappearance of clot, thus enhance recurrent thrombosis. Although fibrinolysis as the first step treatment and surgery in failed thrombolytic therapy carry their own risks, anticoagulant intensification alone in chronic valve obstruction is associated with poor prognosis. The probability of significant bleeding

such as retroperitoneal hematoma and unusual cerebrovascular events following right-sided thrombolysis in patients with potential sources of emboli should be considered. A meticulous follow-up plan including oral anticoagulant dose adjustment and state-of-the-art imaging evaluations at presentation, early post-operative, and subsequent to thrombolysis is of paramount importance in this setting.

Conflicts of interests

The authors declared no potential conflict of interest with respect to the research, authorship, and/or publication of this article.

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Figure legends

Fig. 1: Response to Therapy and Median Elapsed Time from surgery

Fig. 2: Kaplan-Meier curve for freedom from the first recurrence of thrombosis

Footnote: Kaplan-Meier estimation for freedom from the first recurrence of thrombosis revealed that at the end of the first 2 years regardless of the treatment strategy, 84 % of patients were free of recurrent thrombosis, however this declined to 61%, and 21% at the end of 4, and 10 years respectively. Median follow-up time of =31.1mo (0.53-155.9); the median time for the first recurrence in patients= 85.5mo (95% CI: 41.8-129.2).

Fig. 3: Kaplan-Meier curve for survival rate and freedom from chronic valve dysfunction

Footnote: Kaplan–Meier curve of 10-years survival rate and freedom from chronic valve dysfunction at the end of the first year showed a rate of 93%, while it was 82% after 4 years. The 10-year survival rate and freedom from chronic valve dysfunction was estimated 75%. The median follow-up duration = 37.2mo (0.99-205.3)

Table 1- Baseline Characteristics of study population

Values*	Variables
42/67	Number of patients/episodes
45.5 ± 14.3	Age, years)episodes)
28(66.6%)/47(70.1%)	Female, n (patients/episodes)
1.72 ± 0.21	BSA, m^2 (episodes)
Clinical presentations in episodes	Clinical presentations in episodes
31 (46.3%)	Dyspnea
4 (6%)	Chest pain
18 (26.8%)	Significant edema**
10 (14.9%)	Ascites
12 (17.9%)	Increased JVP
2 (3%)	Hypotension
15 (22.4%)	Reduced click
	NYHA functional class in episodes
14 (20.9%)	I-II
17 (25.4%)	III-IV
Mechanical prosthetic valve in episodes	Mechanical prosthetic valve in episodes
26 (38.8%)	St. Jude Medical
24 (35.8%)	Carbomedics (Standard)
15 (22.9%)	Carbomedics (Orbis)
2 (2.9%)	Unknown
31 (27-33)	Prosthetic valve size***
50 (0.4-276)	Elapsed time from valve surgery, months***

Values*	Variables
Anticoagulation status	Anticoagulation status
2.27 (1.7-3.1)	Admission INR
43 (70%)	Sub-therapeutic INR <3
52 (82%)	Sub-therapeutic INR <3.5
48 (71.6%)	Aspirin use
TV pathology in patients	TV pathology in patients
28 (66.6%)	RHD
12 (28.5%)	CHD
2 (4.7%)	IE
Concomitant valvular surgeries in patients/episodes	Concomitant valvular surgeries in patients/episodes
25 (59.5%)/41 (61.1%)	MVR
11 (26.1%)/17 (25.3%)	AVR
4 (9.5%)/11(16.4%)	Redo TVR
Other comorbidities	Other comorbidities
6 (14.3%)	Hypertension
2 (4.8%)	Diabetes mellitus
1 (2.3%)	Coronary artery disease
1 (2.3%)	Prior cerebrovascular events
38 (56.7%)	Atrial fibrillation in episodes
9 (21.4%)	Permanent pacemaker in patients

* Data are presented as numbers (%), mean ± SD, or median (interquartile range). The percentages are based on the total number of episodes or patients and it can differ among variables.

** Significant edema was defined as those with [?]3+

*** It is presented as median (minimum-maximum)

Abbreviations: AVR= aortic valve replacement; BSA = body surface area; CHD = congenital heart disease; IE = infective endocarditis; INR = international normalized ratio; JVP = jugular venous pressure; MVR = mitral valve replacement; NYHA= New York Heart Association; RHD = rheumatic heart disease; TV =tricuspid valve; TVR= tricuspid valve replacement**Table 2-** Echocardiographic findings before and after treatment

	Before treatment	After treatment	p value
Mean gradient, mmHg	10 ± 3.5	4.3 ± 2.7	<0.001
Pressure half-time, msec	407.6 ± 256.6	139.7 ± 109.2	<0.001
Type of thrombus			
Obstructive	65 (97%)	14 (25.5%)	0.04
Non-obstructive	2 (3%)	10 (18.5%)	0.04
Thrombus diameter, cm *	1.13 (0.10 - 3)	0.67 (0 - 2)	0.06
Thrombus area, cm^2 **	0.9 (0.11 - 2.42)	0.4 (0 - 1.14)	0.31
LVEF%	45.3 ± 6.3	46.5 ± 5.7	0.57
Transvalvular leak			0.013
Mild	2 (4%)	8 (40%)	
Moderate	27 (54%)	3 (15%)	
Severe	9 (18%)	0	
RVEF			0.41
Mild	2 (3.2%)	2 (3.7%)	
Mild to moderate	13 (20.6%)	3 (5.6%)	

	Before treatment	After treatment	p value
Moderate	25 (39.7%)	30 (55.6%)	
Moderate to severe	11 (17.5%)	9 (16.4%)	
Severe	12 (19%)	10 (18.5%)	
Mean PAP (mmHg)	30.7 ± 11	25 ± 9.4	0.50

Data presented as numbers (%), or as mean ± SD, or median (interquartile ranges).

* It was available in 29 episodes

** It was available in 20 episodes

Abbreviations: LVEF = left ventricular ejection fraction; RVEF = right ventricular ejection fraction; PAP= pulmonary artery pressure

Table 3- Time interval between recurrence and previous intervention

Previous Intervention	Recurrent episodes, n	Mean time to recurrence mo.*	p value
Thrombolytic therapy	10	13.2 (5.8-20.5)	<0.001
Anticoagulant intensification	8	24.7 (0.5-48.0)	
Redo surgery	6	66.0 (36.8-95.1)	

* Data are presented as mean (95% confidence interval)