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Comparative study between thrombolytic therapy and surgery in 30 cases of acute left sided prosthetic valve thrombosis

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ABSTRACT

Introduction: Prosthetic valve thrombosis is a potentially life-threatening complication associated with high morbidity and mortality. Transthorasic and transoesophageal echocardiography play an important role to the diagnosis and provides incremental information about the optimal treatment strategy. Guidelines differ on whether surgical treatment or fibrinolysis should be the treatment of choice for the management of left-sided prosthetic valve thrombosis. The aim of the study is to compare between thrombolytic therapy and surgery regarding success, morbidity and mortality in the ICU in 30 patients presenting with acute valve thrombosis.
Patients and methods: Our study was constructed as a prospective study that enrolled 30 patients who were divided into 2 groups; Group A which includes 15 patients for whom thrombolytic therapy was delivered, and Group B which includes another 15 patients who underwent a redo surgery. After admission and full history, examination and ECG analysis a written consent is attained for thrombolysis, if not contraindicated, or surgical intervention. Patient assessment by TTE, TEE and occasionally fluoroscopy is done pre-treatment and data is followed up through the ICU course.
Results: There was no statistically significant difference of clinical characteristics between the two groups. Improvement of hemodynamics was more pronounced in group B than group A (86.7% vs. 73.3%, p=0.04). Still, within group A, majority of patients (10/15) improved to NYHA class I and II (p=0.002). There was no statistically significant difference between the two groups regarding duration of mechanical ventilation (p=0.4), inotropc support (p=0.3) or ICU stay (p=0.4). Mortality rate was similar in both groups (p=0.7).
Conclusion: Thrombolytic therapy is a suitable and safe alternative to operation in the majority of patients presented with acute left prosthetic valve occlusion. The management could depend on thrombus burden and location, NYHA functional class of the patient, the presence of embolism, the availability of surgery, the possible contraindications of each therapeutic option, and the clinician's experience.

Key words: Prosthetic valve thrombosis, Transthorasic, transoesophageal echocardiography.

INTRODUCTION

Prosthetic valve obstruction (PVO) is an infrequent but serious complication in patients with prosthetic heart valve and is associated with significant morbidity and mortality [(1,2)]. It is frequently related to thrombus formation, secondary to pannus formation, and rarely to vegetation [(3)]. Prosthetic valve thrombosis (PVT) has an incidence between 0.1% to almost 6% per patient-year of left-sided valves and up to 20% of tricuspid valves [(1, 2, 4)]. PVT depends on valve type, anticoagulation status, valve position, the presence of atrial fibrillation, and/or ventricular dysfunction. The most common cause is an inadequate anticoagulant therapy.

Trans-thoracic (TTE) and trans-esophageal (TEE) echocardiography play an important role to the diagnosis and provides incremental information about the optimal treatment strategy, while fluoroscopy and cardiac computed tomography may be of added value. Guidelines differ on whether surgical treatment or fibrinolysis should be the treatment of choice for the management of left-sided prosthetic valve thrombosis and these uncertainties underline the need for further prospective randomized controlled trials [(3)].

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Thrombus size, New York Heart Association functional class of the patient, the possible contraindications, the availability of each therapeutic option and the clinician's experience are important determinants for the management of prosthetic valve thrombosis [3].

Aim of the Study:

To compare the success, morbidity and mortality of thrombolytic therapy versus surgery, in 30 patients presenting with acute valve thrombosis.

PATIENTS AND METHODS

This is a prospective study that enrolled 30 patients who presented to NHI with acute left sided valve thrombosis. All patients were subjected to full detailed history (including NYHA class, history of embolization, change in metallic sound intensity, and anticoagulation therapy), full clinical examination (including hemodynamics, heart sounds, pulmonary and systemic manifestations of congestion and signs of infective endocarditis), routine laboratory testing, ECG, Chest X-ray, TTE and TEE for assessment of the mobility of valve leaflets, peak gradient (PG), paravalvular leakage and presence of thrombi. The size of the thrombus was determined by plannimetery and categorized into small (<0.5 cm), intermediate (0.5-0.8 cm) and large (>0.8 cm, which was not feasible for thrombolytic). Fluoroscopy was used for assessment of valve mobility. Immobile leaflets, or reduction more than 25% of expected range would suggest prosthetic valve thrombosis.

Patients were divided into 2 groups; Group A includes 15 patients who received thrombolytic therapy, and Group B includes 15 patients who underwent redo surgery. Patients would be initially offered thrombolytic therapy unless the duration from onset of symptoms is more than 2 weeks, thrombus size is more than 0.8 cm, or there was left atrial thrombus, suspected infective endocarditis, absolute contraindication to thrombolysis, or patient preference for redo surgery. In that case patient would undergo redo surgery.

Before commencing treatment, a full written informed consent was obtained from all patients. In group A, thrombolysis was given according to the prolonged slow infusion protocol of Streptokinase (SK) in a dose of (250.000-500.000 unit) over 30 min then 100.000 units per hour for up to 72 hours. Patients were monitored clinically and by serial echo (for thrombus disappearance and PG) and fluoroscopy (for opening and closing angel).

The duration of SK infusion varied according to improvement of hemodynamics, disappearance of thrombus by TEE or return of PG to normal or near normal range. Complete success of thrombolysis was considered when both leaflets opened to normal angel or PG returned to normal. Partial success defined as improvement of hemodynamics associated with drop of PG, short of near normal values. Failure was considered in cases of death, clinical deterioration, or development of complications (embolization or bleeding). When possible, patients who failed thrombolysis were directed to surgery.

Anticoagulation was started after thrombolytic therapy (when there was no bleeding) using weight-adjusted unfractionated heparin (UFH) infusion targeting aPTT 2-2.5 the control time, and Warfarin aiming at INR of 3-3.5. Once INR was in target rang, UFH infusion was stopped. Aspirin at 75-150 mg per day was given to all patients. Clopidogrel 75 mg per day was given when aspirin was contraindication.

In group B, surgery involved replacing the affected valve by either tissue valve or prosthetic valve. Patients were closely monitored perioperatively for any complications.

Statistical Analysis:

Statistical analysis was done using Statistical Package for Social Sciences (SPSS) software, release 16.0.0 for Windows™ (SPSS Inc., Chicago, Illinois). Quantitative variables were described using mean ± standard deviation (SD) if they were normally distributed, and median and inter-quartile range (IQR) if data was skewed. Categorical variables were described using frequencies and percentages. Bivariate analysis of categorical variables was done using Chi Square test. Comparing two groups of quantitative variable was done using Independent Samples Student t test for parametric data, and Mann-Whitney test for nonparametric one. Paired data was compared using paired Student t test when parametric, Sign test when non-parametric, and McNemar's test when categorical. In all cases, the 2-sided significance was always taken as p value, and a p value less than 0.05 was considered statistically significant.

RESULTS

Patients were divided into two equal groups; group A (15 patients), who received SK by long course protocol as first line of therapy and group B (15 patients), were treated surgically by prosthetic valve re-replacement. The demographic and clinical characteristics of both groups are listed in Table-1.

In all patients, the stuck valve was the prosthetic mitral valve. There was no statistically significant difference regarding prosthetic valve type, site or duration of insertion. The type of used anticoagulant, adequacy of and compliance to anticoagulation was also similar in both groups. The same is observed for number of previous redo surgeries.

History of previous events of arterial embolization or venous thrombosis was also similar in both groups (Table-2).

All patients underwent transthoracic (TTE) and

Table-1. Demographic and clinical characteristics of study groups.

Clinical characteristics	*Thrombolytic (Group A) n=15*	*Surgery (Group B) n=15*	*P value*
Age (mean±SD)	36.6 ± 11.4	35.1 ± 11.9	0.7
Female (n, %) Pregnancy (n, % of females) IUFD (n, % of pregnancy)	6, 40 3, 50 0	11, 73 3, 27 3, 100	0.1 0.6 **0.01**
Type of prosthetic mitral valve (n, %) Bileaflet Monoleaflet	 15, 100 0	 14, 93.3 1, 6.7	NS
Duration since implantation, in years (mean, range)	8, 3-11.5	3, 1-8	NS
Anticoagulation used (n, %) UFH Warfarine LMWH UFH + Warfarine + Asp +Clop	 3, 20 11, 73.3 0 1, 6.7	 3, 20 9, 60 1, 6.7 2, 13.3	NS
Anticoagulation adequacy (n, %) Good Bad	 3, 20 12, 80	 2, 13.3 13, 86.7	NS
Compliance (n, %) Compliant Non compliant	 4, 26% 11, 74%	 3, 20% 12, 80%	NS
aPTT(mean±SD)	36.2 ± 8.0	33.3 ± 6.2	NS
INR (mean±SD)	1.3 ± 0.3	1.2 ± 0.2	NS
Previous redo surgeries (n,%) 0 1 2 3 4	 12, 80% 1, 6.7% 1, 6.7% 1, 6.7% 0	 10, 66% 3, 20% 1, 6.7% 0 1, 6.7%	NS

IUFD: Intra Uterine Fetal Death, NS: non-significant, UFH: Unfractionated Heparin, LMWH: Low Molecular Weight Heparin, Asp: Asprin, Clop: Clopidogrel, aPTT: activated Patial Thromboplastin Time, INR: International Normalization Ratio.

Presenting hemodynamics

All patients in both groups had inaudible clicks of their metallic mitral valve on presentation. The duration of symptoms was shorter in group A (mean 12 hours, range 9.0-14.25 hours) than group B (mean 24 hours, range 12-48 hours) with a significant P value of .002. Other presenting hemodynamics are listed in table-3.

Echocardiographic assessment:

trans-oesophageal (TEE) echo on admission. Relevant findings are listed in table-4. The number of patients with thrombi visible by TTE was larger in group B than in group A (5,33,3% vs. 0 respectively, p=0.04).

The larger number of patients with LA/LAA thrombi in group B (p<0.001) reflects the fact that thrombolysis was contraindicated in those patients, hence were excluded from group A. For the same reason, initial thrombus size was larger in group B than group A (2.0 ±

1.2 cm vs. 0.5 ± 0.2 cm, *p<0.001)* because patients with large thrombi were not eligible for thrombolysis.

Effects of Interventions:

Hemodynamic improvement was significantly better in group B than group A as 13 patients (86.7%) became vitally stable and 2 patients (13.3%) achieved borderline hemodynamic after surgery, compared to only 11 patients (73.3%) who became vitally stable after thrombolysis (*p*=0.04), figure 1.

Effects of interventions:

Hemodynamic improvement was significantly better in group B than group A as 13 patients (86.7%) became vitally stable and 2 patients (13.3%) achieved borderline hemodynamic after surgery, compared to only 11 patients (73.3%) who became vitally stable after thrombolysis (*p*=0.04), figure 1.

There was a significant improvement in NYHA classification after thrombolytic therapy (*p*= 0.002). Six patients (out of nine patients presented with NYHA class III) improved to NYHA class I, and 2/9 improved to NYHA class II. Two patient (out of six patients presented with NYHA IV) improved to NYHA class I and 4/6 improved to NYHA class II (figure 2).

Duration of mechanical ventilation and inotropic support were similar in both groups. Although ICU length of stay was longer in group A (6 days vs. 4 days), the difference was statistically insignificant (Table-5).

In group A, PG, MG, PASP, and valve area (assessed by TTE) have significantly improved after treatment.

Thrombus size (assessed by TEE) also significantly resolved (table-6).

Table-2. Previous embolic and thrombotic events in study groups.

Venous thrombosis	*Thrombolytic- Group A n=15*	*Surgery- Group B n=15*	*P value*
Previous thrombotic events (n, %) Stroke or TIA DVT Combined DVT & stroke	 4, 30.8 1, 7.7 1, 7.7	 3, 20.0 1, 6.7 2, 13.3	NS
Previous embolic events Stoke STEMI LL Ischemia	 1, 6.7 1, 6.7 0	 3, 20.0 0 1, 6.7	NS

TIA: Transient ischemic attack. DVT: Deep Venous Thrombosis, STEMI: ST segment Elevation Myocardial Infarction, LL: Lower limb.

Table-2. Hemodynamics on presentation

Hemodynamics	*Thrombolytic (Group A) n=15*	*Surgery (Group B) n=15*	*P value*
Heart Rhythm (n, %) Sinus rhythm AF PM	 9, 60 6, 40 0	 8, 53.3 6, 40 1, 6.7	NS
Hemodynamics on presentation (n, %) Borderline Hemodynamics Frank shock	 8, 53.3 7, 46.7	 7, 46.7 8, 53.3	NS
Unstable patients on presentation (n, %) unstable Stable	 8, 53.3 7, 46.7	 9, 60 6, 40	NS
Cause of instability on presentation (n, %) Severe pulmonary edema Cardiogenic Shock Status Epilepticus Severe PE & Cardiogenic Shock	 0 1, 12.5 1, 12.5 6, 75	 2, 22.2 1, 11.1 0 6, 66.7	NS
NYHA class (n, %) Class III Class IV	 9, 60 6, 40	 7, 46.7 8, 53.3	NS

AF: Atrial fibrillation, PM: pacemaker, PE: Pulmonary oedema, NS: non-significant.

Complication rate was similar in both groups. Infections and need for renal replacement therapy was higher in group B while mortality rate was higher in group A. However, the differences did not reach statistical significance (Table-7).

DISCUSSION

Prosthetic valve obstruction (PVO) is an infrequent but serious complication in patients with prosthetic heart valve and is associated with significant morbidity and mortality [1, 2].

PVT is mostly a complication of mechanical valves, while pannus formation is common to both bioprostheses and mechanical valves [3].

Reasons for the increased thrombogenicity of mechanical valves are the interaction of blood constituents such as platelet and blood cells first with injured endocardium immediately after the surgery,

Table-4. Echocardiographic Measurements on initial presentation

Echocardiographic Measurements	*Thrombolytic (Group A) n=15*	*Surgery (Group B) n=15*	*P value*
Thrombus detected by TTE (n, %)	0	5, 33.3	0.04
LA size in cm (mean ± SD)	5.7 ± 0.8	6.0 ± 0.7	0.3
LV function (EF%) (mean ± SD)	50.7 ± 13.6	56.3 ± 9.1	0.2
PG in mm Hg (mean ± SD)	43.9 ± 9.9	39.1 ± 8.6	0.2
MG in mm Hg (mean ± SD)	21.5 ± 3.8	18.2 ± 1.9	0.2
PASP in mm Hg (mean ± SD)	67.5 ± 15.5	59.6 ± 9.1	0.1
Valve area in cm^2 (mean ± SD)	0.63 ± 0.12	0.71± 0.17	0.2
LA or LAA thrombi (n, %) LA LAA Both LA and LAA	 0 0 0	 1, 6.7 9, 60.0 2, 13.3	<0.001
Presence of pannus (n, %)	6, 40.0	4, 28.6	NS
Thrombus detected by TEE (n, %)	15, 100	15, 100	NS
Thrombus size on presentation in cm (mean ± SD)	0.5 ± 0.2	2.0 ± 1.2	<0.001

TTE: Transthoracic echo, LA: left atrium, LV: left ventricle, PG: peak gradient, MG: mean gradient, PASP: pulmonary artery systolic pressure, TEE: Transesophageal echo, LAA: left atrial appendage.

Table-3. Clinical responses after intervention

Clinical Responses	*Thrombolytic (Group A) n=15*	*Surgery (Group B) n=15*	*P value*
Instability after treatment (n, %) unstable Stable	 5, 33.3 10, 66.7	 7, 46.7 8, 53.3	0.7
Duration of IMV In days (mean, range)	1, 0.5-4	2, 1-5	0.4
Duration of inotropic support In days (mean, range)	3, 1-5	1, 0.5-3	0.3
ICU LOS In days (mean, range)	6 (1-10)	4 (3-7)	0.4

IMV: Invasive mechanical ventilation, LOS: length of stay.

Table-6. Changes of Echocardiographic measurements after thrombolysis

Echocardiographic Measurements	*On presentation*	*After thrombolysis*	*P value*
PG in mm Hg (mean ± SD)	43.9 ± 9.9	22.5 ± 15.0	<0.001
MG in mm Hg (mean ± SD)	21.5 ± 3.8	12.2 ± 8.9	0.008
PASP in mm Hg (mean ± SD)	67.5 ± 15.5	51.2 ± 14.1	0.004
Valve area	0.63 ± 0.12	1.5 ± 0.6	<0.001
Thrombus size (TEE)	0.5 ± 0.2	0.1±0.01	<0.001

PG: peak gradient, MG: mean gradient, PASP: pulmonary artery systolic pressure, TEE: Transesophageal echo

Table-7. Complications of interventions

Complications	*Thrombolytic (Group A) n=15*	*Surgery (Group B) n=15*	*P value*
Infection (n, %)	1, 6.7	5, 33.3	0.2
Need for RRT (n, %)	0	2, 13.3	0.5
Mortality (n, %)	4, 26.7	2, 13.3	0.7

RRT: Renal replacement therapy

secondly with the surface of the mechanical valve that has thrombogenic properties leading to both platelet deposition and activation of factor XII, and thirdly with structural and metabolic changes due to irregular flow patterns arising around the prosthetic devices [5, 6]. Thrombus formation usually begins at the hinges of mechanical valves [7]. Increased incidence of thrombotic events up to 10% have been reported in the first 3−6 months after implantation of the valve mainly in the mitral position. This can be explained by the hypercoagulable state after surgery and the contact of bloodstream with the nonendothelialized thrombogenic surfaces particularly on suture sites and prosthesis material [8]. Bioprosthetic valves have a considerably less frequency of thrombosis, approximately 0.03% per year mainly seen in the first months following surgery while the sewing ring becomes endothelialized [9, 10].

After prosthetic valve endothelialization, inadequate level of anticoagulation is the most important factor involved in the pathogenesis of prosthetic valve thrombosis, adding to this many other factors including the site, and type of the prosthesis, the hypercoagulable state, the cardiac morphology and function [11].

Operation with either valve replacement or thrombectomy with debridement was considered the treatment of choice for acute PVT, however operation in this situation is most demanding technically, often performed under urgent circumstances regardless of all the re-operation-related risks with operative mortality of 19.6% for repeat mitral valve replacement. Surgical valve debridement is occasionally sufficient and may be associated with a lower operative mortality [12], although the rate of rethrombosis may be significantly higher [13].

Re-operations are technically more difficult than primary operations because of adhesions around the heart and the common association of pulmonary hypertension with valve dysfunction. Also, replacement operations are often performed in functionally compromised patients who tolerate complications poorly or have little reserve. In the past, redo valve surgery has been associated with a considerably higher operative mortality than primary valve surgery, particularly in patients who have had multiple prior replacements. However, in the modern era there has been some improvement in both morbidity & mortality [14].

In our study double valve replacement was done in six patients meanwhile the stucking valve was only the mitral and this could be explained by the low blood flow velocity upon the mitral which is less than the flow velocity upon the aortic valve. The flow velocity over the tricuspid valve is lower than the mitral valve, so the highest incidence for PVT is on the prothetic tricuspid (not included in this study) then the prothetic mitral and it is the least common in the aortic valve prothesis.

This goes with the meta-analysis done by *Esteban Rayez Cerezo et al* which included 904 patients, 78% of the stucking was due to mitral valve thrombosis [15].

In a meta-analysis published in 1994 with 13,000 patients with metallic prosthesis, the annual incidence of thrombosis was 0.2%, with thromboembolic events

Figure-1. Hemodynamics after treatment

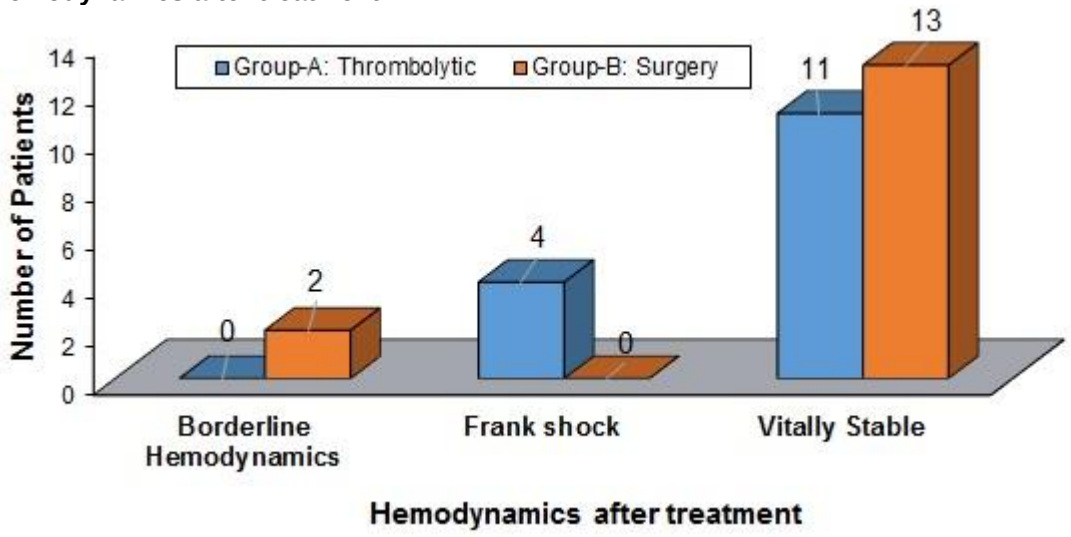
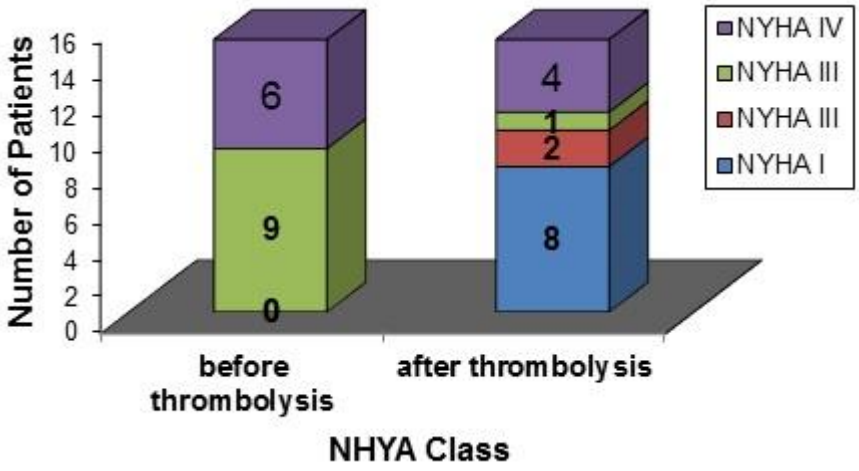


Figure-2. NYHA class before and after thrombolysis



occurring at a rate of 1.8% per year. According to that study, in regard to location, patients with mitral prosthesis had a 2-fold greater risk for thrombosis than those with aortic prosthesis, and the metallic prosthesis in the tricuspid position had the greatest thrombogenicity. In addition, the caged metallic prosthesis was the most thrombogenic, ***(****Tong AT et al 2004),* and this goes with our study results [16].

Traditional therapy of left-sided OPVT is emergency surgery (valve replacement or thrombectomy), but thrombolysis has been proposed as an attractive first-line alternative [17, 18]. The optimal management remains unclear because there is lack of randomized controlled trials to compare the two methods. Additionally the published guidelines differ significantly on whether surgery or thrombolysis should be the treatment of choice, as well as on which is the main determinant for the treatment (functional class, thrombus size, obstructive, or nonobstructive thrombosis) [18, 20-21].

According to the 2007 European Society of Cardiology (ESC) [22] and the 2008 American College of Cardiology/American Heart Association (ACC/AHA) [23] guidelines, surgery is the treatment of choice of left-sided OPVT [18, 19]. The drawback of surgery is the high operative mortality (between 5% and 18%) which is largely related to clinical functional class, with New York Heart Association (NYHA) functional class at presentation to be a strong predictor of surgical mortality (4−7% in class I−III vs. 17.5−31.3% in class IV) [24, 25]. Thrombolysis followed by heparin infusion has been suggested as an alternative to surgery. It is associated with lower mortality rate but carries the risk of systemic embolism, bleeding, and rethrombosis.

In concordance to our study, Roudaut et al. [1] in the largest single-centre nonrandomized retrospective

study, cited better early success rate and a significant lower incidence of complications for post-surgical than post-fibrinolytic therapy in left-sided OPVT. There was no difference between the two groups in terms of mortality (10%). However, complete haemodynamic success was significantly more frequent in the surgical group (81% vs. 70.9%) and embolic episodes were significantly more frequent in fibrinolysis group (1% vs. 0.7%), as were total complications (25% vs. 11.1%). The authors proposed thrombolysis as first-line therapy in cases of critically ill patients whose operative risk is high or if surgery cannot be performed urgently (rescue fibrinolysis).

On the other hand, more recent studies [26, 27] show that fibrinolytic therapy can restore adequate function of the thrombosed prosthetic valve with high rates of success and lower mortality and complication rates than those reported by Roudaut et al. [1] mainly in the post-TEE era. On this basis, thrombolysis is recommended as the first-line treatment for all patients with left-sided PVT by the Society for Heart Valve Disease (SHVD) guidelines and for patients with low thrombus burden (<0.8cm2) regardless of functional class by the American College of Chest Physicians (ACCP) guidelines [28].

In our study NYHA IV was unremarkably higher in the surgical group that may show discordance with other studies reported that patients in NYHA IV class presented significantly less mortality post thrombolysis (7%) than did post-surgery (17%) [1] while there was no difference in our study.

The success rate in our study was discordant with The full success rate in other eastern studies. *Reddy et al*, [29] reported 88.6% success rate among his 44 episodes, *Kumar et al*. [30], reported 87.5% success rate among 48 episodes, and *Gupta et al.* [31], reported 91.8% success rate that may be due to the smaller number in our study group.

On the other hand our study results were concordant with the study of *Witchitz et al.* [32] who reported 70% success rate and *Roudaunt et al.* [1] who reported 75% success rate.

CONCLUSION

Thrombolytic therapy is a suitable and safe alternative to surgery in the majority of patients presented with acute prosthetic valve occlusion, it was shown to be nearly equal, and it might appear to be the optimal therapeutic choice in the majority of patients with PVT. TEE is recommended in the management of prosthetic valve thrombosis because it can identify low-risk groups for thrombolysis, and identify proper candidates for thrombolysis.

The management depends on thrombus burden and location, NYHA functional class of the patient, the presence of embolism, the availability of surgery, the possible contraindications of each therapeutic option, and the clinician's experience.

The remaining uncertainties in many aspects of the therapy of patients with PVT underline the need for future randomized controlled trials.

Conflict of Interests

Authors declare that there is no conflict of interests regarding the publication of this paper.

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