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Research Article

Therapeutic Thrombolysis of Mechanical Prosthetic Valve Thrombosis Using Reteplase: An Effective and Safe Treatment Modality

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Abstract

Objective: Emergency redo surgery for stuck valve or prosthetic valve thrombosis (PVT) has higher mortality rates and thrombolytic therapy has been proven effective treatment with different thrombolytic agents. In this study we evaluated the efficacy and safety profile of thrombolysis using Reteplase.

Materials and Methods: We retrospectively analyzed data of total 124 patients of stuck valve undergone thrombolysis between Jan 2013 t0 Dec 2020, after proper diagnostic evaluation at the time of presentation.

Results: The incidence of stuck valve was 3.65% with mean age of patients was 39.8 ± 11.9 years, mean interval from valve replacement surgery to episode of stuck valve was 4.9 ± 2.7 years. After thrombolysis, 71 (64.6%) patients had full range reopening of valve leaflets, 27 (24.5%) patients had partial reopening of leaflets, failed thrombolysis in 08 (7.3%) patients. As complications, 06 (5.4%) patients developed major bleeding, 16 (14.5%) patients developed minor bleeding, 08 (7.2%) patients developed cerebrovascular stroke and 04 (3.6%) patients expired.

Conclusion: Because of good efficacy, better safety, easy dosing Reteplase can be considered as an effective thrombolytic agent in patients with stuck bileaflet valve.

Keywords: *Prosthetic Valve Thrombosis (PVT); Reteplase; Thrombolysis; Redo Surgery*

Introduction

Mechanical prosthetic valve thrombosis (PVT) is associated with substantial morbidity and mortality with incidence varying from 0.3 to 1.3% patient years [1], especially in patients with poor compliance to anticoagulation therapy followed by thrombotic states like pregnancy, atrial fibrillation and ventricular dysfunction [2]. According to the new guidelines for the management of valvular heart disease, fibrinolytic therapy is considered the best choice of treatment in the right-sided PVT [3]. A repeat operation carries a substantial risk, with mortality rate ranging from 10% to 15% in selected series which may be two- or three-fold higher in critically ill patients [4]. Bi-leaflet valves are more prone because of their delicate mechanism leading to more easily to leaflet immobilization, even with a relatively small clot [5]. In patients with left-sided prosthetic valve thrombosis with dyspnea, New York Heart Association (NYHA) class 3 and 4 either intravenous streptokinase or surgical valve replacement can be considered depending upon the surgical risk with thrombolysis preferred in patients who are at a higher surgical risk. Redo surgery is an option for those patients in which the prosthetic valve has a heavy thrombus burden and the patient is hemodynamically stable enough to tolerate cardiopulmonary bypass [6]. In 1971, Luluaga., *et al*. were the first to use the thrombolytic therapy in PVT [7]. Streptokinase was used for treating thrombosis of the tricuspid valve prosthesis. Three years

later, Baille., *et al*. reported the use of thrombolytic agent in a patient with aortic PVT [8]. Guidelines are divided over the best line of therapy with some (European Society of Cardiology) recommending surgery for all, irrespective of clinical status, while others (society of heart valve diseases) recommend thrombolytic therapy for all patients without contraindications. In India and other developing countries, thrombolytic therapy is an attractive and easy option due to high cost and unavailability of surgery on emergency basis in many centers. Urokinase and tissue plasminogen activator (tPA) have previously been used with success and their efficacy was assessed and validated [9]. The first-line thrombolytic agent for obstructive PVT is recombinant tissue plasminogen activators (r-TPA) or streptokinase, but recombinant plasminogen activators (r-PA), such as Reteplase can be used in patients with PVT who cannot use streptokinase or r-TPA with any reason and review of literature shows few small group studies available on Reteplase used for PVT thrombolysis. We report a single center experience of thrombolysis using Reteplase in 124 patients of PVT and analyzed its characteristics, efficacy and complications.

Materials and Methods

Because emergency redo surgery is associated with higher mortality in cases of prosthetic valve thrombosis, thrombolytic therapy was used as the first option to treat those cases in our hospital which is a tertiary care hospital and surgery was performed for the patients who had contraindication to thrombolysis or the patients in whom thrombolysis failed [2]. Data of total 124 patients with stuck valve (prosthetic valve thrombosis) were retrospectively analyzed who underwent thrombolysis between January 2013 to December 2020. The patients were included as per inclusion criteria:

- All symptomatic patients with obstructive stuck valve diagnosed by clinical examination, TTE and Cinefluoroscopy.
- Patients with asymptomatic non-obstructive stuck valve with a thrombus diameter < 10 mm or 0.8 cm^2.
- Stuck valve patients with ischemic stroke only if they were stable by neuroradiological assessment after 6 weeks of anticoagulation (patients without hemorrhagic stroke and/or severe disability).

Patients were excluded as per exclusion criteria:

- Patients with a contraindication to thrombolytic treatment as described in table 1.
- Patients with asymptomatic nonobstructive stuck valve without a history of recent thromboembolism and with a thrombus diameter of > 10 mm or 0.8 cm^2.
- Patients with stuck valve who had no thrombus/mass/pannus on transthoracic echocardiography and had normal prosthetic valve leaflet motion on fluoroscopy considered patient-prosthesis mismatch.
- Patients with recurrent stuck valve following thrombolytic therapy.
- Patients having International normalized ratio (INR) > 2 on presentation.

Absolute Contraindications	Relative Contraindications
Left atrial thrombus	Active peptic ulcer
Recent (< 3 weeks) ischemic stroke	Blood pressure > 180/110 mm Hg
Early (< 4 days) post-operative period	Recent (< 4 wk) internal bleed
Traumatic accident < 4 weeks	Previous thrombolytic therapy (< 3 months)
Bleeding diathesis or INR > 2	Recent Cardiopulmonary resuscitation
Intracranial mass	Infective endocarditis
Active internal bleed	Hemorrhagic retinopathy, pregnancy
Aortic dissection	Pericarditis

Table 1: *Contraindications of thrombolytic therapy.*

On presentation with clinical suspicion of stuck valve, intravenous Heparin 5000 IU was administered to each patient as an institutional protocol and were subjected to further tests including international normalized ratio (INR) level, transthoracic echocardiogram (TTE), trans esophageal echocardiography (TEE) in doubtful cases and cinefluoroscopy. Patients' symptoms were recorded expressed as dyspnea New York Heart Association (NYHA) class, embolic phenomena (peripheral, coronary, cerebral) anginal pain, palpitations and syncope. Transthoracic echocardiogram (TTE) was performed in all clinically suspected cases to determine the peak and mean transvalvular gradient and presence of valve leaflet opening and closing clicks. Confirmation of stuck valve was made by cinefluoroscopy, taken in side/pivot view with discs parallel to x-ray beams. The anticoagulation status was observed from trend of previous international normalized ratio (INR) values and doses of anticoagulants taken by the patients. For description the following definitions were adopted:

- **Stuck valve:** Inability of valve leaflets to move in full range fully, according to the manufacturer's definitions and previously studied normal range [10].
- **Thrombolytic course:** Administration of a single thrombolytic agent in its prescribed dosage.
- **Full valve reopening:** Regaining normal range motion of valve leaflet on cinefluoroscopy with improvement of valve gradient on echocardiography.
- **Partial valve reopening:** Achievement of improved but less than full range of motion of valve leaflet.
- **Failure:** No clinical improvement, which included death or complications like major bleeding or systemic embolism requiring termination of thrombolytic therapy.

Once prosthetic valve thrombolysis (stuck valve) was confirmed, the patient and attendants were counseled in details regarding need, procedure, possible outcomes and complications of medical thrombolysis therapy with informed consent for the same. The patient were offered thrombolysis therapy as intravenous administration of Reteplase with a bolus dose of 10 units (18 mg) stat over 2 minutes followed by another bolus dose of 10 units (18 mg) within half an hour of the first dose after necessary precaution measures taken. Thrombolytic therapy was continued till valve reopening on TTE or for at least 24 hours. Thrombolytic therapy was stopped if there was any evidence of major thromboembolic episode or hemorrhagic complications or in treatment failure cases. Treatment failure was considered when even after 24h of therapy there was no improvement in transvalvular gradient or valve leaflet mobility or patient deteriorated clinically. These cases were taken up for redo surgery after urgent preoperative preparation. In patients who demonstrated a favorable response to thrombolytic therapy, thrombolysis was continued till TTE gradient became normal with improvement in valve leaflet opening. This was followed by subcutaneous LMWH (Enoxaparin) or Fondaparinux and simultaneous oral Warfarin or Acenocoumarol to achieve target INR (3.0 - 3.5) levels with Aspirin (75 mg/day). TTE was done to assess gradients across the prosthetic mechanical valve. Evaluation of efficacy of thrombolytic therapy was analyzed from the post thrombolysis clinical response, TTE and by cinefluoroscopy. The post-thrombolysis complications were also noted and managed accordingly.

Results

Over a period of 7 years (January 2013 to December 2020), total 3396 patients underwent bi-leaflet valve replacement surgery at our hospital and total 124 patients presented with stuck valve with incidence of 3.65%, out of which 110 patients were given thrombolytic therapy and 14 patients were excluded from the study as per inclusion and exclusion criteria. The no. of cases and their demographic characteristics are mentioned in table 2. Out of those 124 cases, males were 50 (45.5%) and females were 60 (54.5%) in number and the mean age was 39.8 ± 11.9 years. During initial presentation, 77 (70%) patients had atrial fibrillation (AF) and 33 (30%) patients had normal sinus rhythm. The mean interval from valve replacement surgery to episode of stuck valve was 4.9 ± 2.7 years with 03 (2.7%) cases presenting within 1 year and 106 (96.3%) cases after 1 year of valve replacement. On taking history and analysis of compliance to oral an-

ticoagulants, 65 (59.1%) patients revealed taking oral anticoagulants irregularly in dose or timing. The mean duration of symptoms while presentation to hospital was 5.6 ± 2.9 days. On the basis of symptoms of dyspnea and congestive heart failure, 15 (13.5%) patients were in NYHA class I-II, 36 (32.7%) patients in NYHA class III and 59 (53.7%) patients in NYHA class IV. Any bleeding that necessitated blood transfusion or was associated with a decrease of 2 g/dl or more in blood hemoglobin concentration was considered as major bleeding event [5]. Otherwise, bleeding was termed minor. A detailed neurologic examination and brain computed tomography were performed in the patients who had neurologic complaints during or after the thrombolytic therapy. We observed total 34 (30.9%) patients developed complications of thrombolytic therapy out of which 06 (5.4%) patients developed major bleeding, 16 (14.5%) patients developed minor bleeding, 08 (7.2%) patients developed cerebrovascular stroke and 04 (3.6%) patients expired. After thrombolytic therapy, we found 71 (64.6%) patients had full range reopening of valve leaflets, 27 (24.5%) patients had partial reopening of leaflets and 08 (7.3%) patients had no response considered as failure of thrombolysis.

Total patients with bileaflet valve	3396
Total no. stuck valve cases	124
Patients thrombolysed	110
Patients not included in study	14
Incidence of PVT	3.65%

Table 2: *No. of cases thrombolysed and their incidence.*

Total no. of cases thrombolysed	110
Age (years)	39.8 ± 11.9
Males	50 (45.5%)
Females	60 (54.5%)
Base line sinus rhythm	33 (30%)
Atrial fibrillation	77 (70%)
Mean time from surgery to thrombosis (years)	4.9 ± 2.7
Within 1 year	03 (2.7%)
After 1 year	106 (96.3%)
Compliance to oral anticoagulants	45 (40.9%)
Noncompliant to oral anticoagulants	65 (59.1%)
Mean time of presentation (days)	5.6 ± 2.9
Initial NYHA class	15 (13.5%)
I-II	36 (32.7%)
III	59 (53.7%)
IV	

Table 3: *Patient's demographic characteristics during admission.*

Death	04 (3.6%)
Major bleeding	06 (5.4%)
Stroke (cerebrovascular accidents)	08 (7.2%)
Minor bleeding	16 (14.5%)
Total	34 (30.9%)

Table 4: *Complications of thrombolytic therapy.*

Full valve reopening	71 (64.6%)
Partial valve reopening	27 (24.5%)
Failure	08 (7.3%)
Death	04 (3.6%)

Table 5: *Result of thrombolytic therapy.*

Discussion

Bileaflet valves are the mechanical valves of choice and widely used at the present. Different bileaflet valve models have different propensities for thrombosis and it also depends on many other factors. There are conflicting opinions regarding the size of the thrombus and how it should affect the feasibility of thrombolysis. Hurrell., *et al*. considered a large (0.5 mm) left sided thrombus as a contraindication to thrombolysis [11]. Lengyel., *et al*. considered a large thrombus as a relative contraindication to thrombolysis, but no cut-off point was given [12]. On the other side, Vitale., *et al*. considered a visible clot on TEE as one of the diagnostic criteria essential to the establishment of prosthetic valve thrombosis. In our study we included patients with asymptomatic non-obstructive stuck valve with a thrombus diameter < 10 mm or 0.8 cm^2 according to ACC AHA 2014 guidelines.

Fibrinolytics are divided into two categories: fibrin specific and non-fibrin specific. Streptokinase is a non-fibrin-specific fibrinolytic but reteplase or r-PA and alteplase or r -PA are both included in fibrin-specific group. The studies showed that both rt-PA and streptokinase can be used as first-line medication in PVT. Cardiologists usually prefer to use streptokinase as first-line medication because it is older and there is more experience with it, but streptokinase is highly antigenic and it can cause allergic reaction after first administration [13]. On review of literature, evidence for the use of Reteplase as thrombolytic agent for prosthetic valve thrombosis remains sparse and it is not widely accepted for the purpose. Reteplase is a third generation thrombolytic agent and is a recombinant human tissue plasminogen activator, widely used in occlusive thrombotic disorders such as myocardial infarction [14]. Long half-life, lack of need for weight based dose adjustment, bolus injection instead of infusion, rapid onset of action, and lower rates of serious complications such as bleeding and fibrinogen depletion have made it an ideal thrombolytic agent.

Over a period of 7 years, the incidence of stuck valve in our study we found to be 3.65% and other studies reported incidence of 0.03% in bioprosthetic valves, 0.5% to 8%in mechanical valves in the mitral and aortic positions, and as high as 20% in mechanical tricuspid valves [15,16]. Singh AK., *et al*. in his case series found that the mean interval between thrombosis episode and valve implantation was 3.2 years at mitral position (range 3 months to 12.4 years) similar to our finding of 4.9 years on average out of which 2.7% cases presented within 1 year [17]. One of the main reasons for this high incidence is the low socioeconomic and low education status of most of the patients causing poor compliance of oral anticoagulation therapy. In our study, 59.1% of the patients either had poor compliance with oral anticoagulation therapy. Similar results were found in another study in which 55.50% of the patients had suboptimal INR and 20.90% of the patients were non-compliant with warfarin therapy [18]. Torrado E., *et al*. showed 80% of total response to therapy, 8% of incom-

plete resolution, 15% embolic complications, 11% hemorrhages and 7% mortality [19]. In our study we found full valve reopening in 71 (64.6%) patients, partial valve reopening in 27 (24.5%) patients and 08 (7.3%) patients had no response to thrombolysis. As complications of thrombolysis, 6 (5.4%) patients had major bleeding, 8 (7.2%) patients had stroke (cerebrovascular accidents), 16 (14.5%) patients had minor bleeding and 4 (4.3%) patients expired. Roudaut and co-workers reported a surgical mortality of 10.3% in 136 patients operated, all in functional class IV [20]. In comparison to redo surgery, thrombolysis is easy to implement, less costly and is associated with a lower mortality rate. Roudat., *et al*. observed Surgery for patients in NYHA class IV was associated with a mortality rate of 17.5% and Deviri., *et al*. observed the same to be 24% [20,21]. The issues not in favor of thrombolysis include risk of systemic embolism, incomplete response to thrombolysis and a relatively high frequency of rethrombosis [22]. Lengyel., *et al.* stated that thrombolytic therapy of left-sided PVT is acceptable for critically ill patients in whom surgical intervention carries high risk or in patients with contraindications to operation [12].

Conclusion

Clinical suspicion of prosthetic valve thrombosis requires prompt diagnostic assessment with echocardiography and cineflouroscopy. Treatment strategy between redo surgery and medical thrombolysis should be judiciously depending on patient's functional status and thrombus burden. Apart from the conventional thrombolytic agents used earlier, intravenous Reteplase can be used effectively in a wide variety of patients, regardless of symptom duration and severity, but surgery may be preferred for hemodynamically compromised patients who may not withstand the delay to surgery. The advantages of Reteplase like minimal antigenicity, rapid thrombolytic activity, comparable efficacy, convenience of dosing and acceptable complication profile makes it a good alternative thrombolytic agent.

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Conflicts of Interest

There are no conflicts of interest.

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