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Case Report

Successful Thrombolytic Treatment of a Thrombosed Mechanical Mitral Valve in a Post-brain Surgery Patient- A Case Report and Literature Review

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ABSTRACT

The first-line management of prosthetic valve thrombosis is not yet finalized; dealing with such cases remains a clinical challenge and requires prompt detection, timely diagnosis and individualized case management regardless of whether the case in question requires a surgical or medical therapeutic approach. We report a unique case of mechanical mitral valve thrombosis post Bentall procedure with a double aortic-mitral valve replacement in a patient who previously underwent brain surgery after experiencing a Road Traffic Accident (RTA). The patient was successfully treated by using a combined loading and infusion regimen of tissue-Plasminogen Activators (t-PA). A small loading dose of 15 mg followed by a low-dose slow infusion of t-PA has been shown to provide effective and safe thrombolysis in high-risk patients with prosthetic valve thrombosis.

Keywords: Mechanical valve thrombosis; Tissue Plasminogen Activators (tP-A); Brain surgery

INTRODUCTION

Prosthetic valve thrombosis constitutes a rare but serious complication of mechanical cardiac valves [1]. Its incidence varies from 0.03%-12% per year [2-4] with mitral valve thrombosis being, on average, five times more common than that of aortic prosthetic valves [4,5]. The risk is from 1.8 per 100 patients per year to less than 0.3 per 100 patients per year by using an optimal anticoagulation treatment procedure based on the timely administration of Warfarin [4]. Since the beginning of valve replacement surgeries in the 1950(s) [6], multiple cases of prosthetic valve thrombosis have been reported. Many authors have proposed various treatment regimens as a means of managing the problem. The solutions that have been proposed thus far range from surgical valve replacement to thrombolytic therapy [3,7-10]. Incidentally, a high clinical suspicion of prosthetic valve thrombosis should prompt confirmation of the condition using appropriate investigations and the involvement of the heart and multidisciplinary team as soon as possible. Despite the magnitude of research done in this field, no uniform mode of management has been agreed upon for the treatment of prosthetic valve thrombosis; whether this is in reference to surgical or thrombolytic therapy, nor has the choice of thrombolytic drug along with its proper dosage prescription has been finalized yet. This may be due to a lack of randomized control trials.

This paper will examine the case of a patient post-Bentall procedure who had had a metallic prosthetic mitral valve installed 2 months earlier and who also had a history of previous brain surgery following a RTA, 14 months before presentation at the hospital. The patient presented with a thrombosed prosthetic mitral valve and was successfully treated with tissue plasminogen activator t-PA, and underwent further anticoagulation therapy using Heparin and Warfarin. To the best of our knowledge, no other case of a similar complexity has been reported in the literature so far.

CASE PRESENTATION

A 35-year-old male patient had suffered a Road Traffic Accident (RTA) resulting in both comminuted and disfiguring craniofacial fractures involving the orbits and the para-nasal sinuses along with the leaking of Cerebro-Spinal Fluid (CSF). His condition required him to undergo decompression craniotomy and the insertion of Ventriculo-Peritoneal (V-P) shunts. He was bed ridden and developed recurrent Deep Venous Thrombosis (DVT) that required the installation of Inferior Vena-Caval (IVC) filter. One year after the RTA, he underwent the insertion of a 31/33 mm

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bileaflet prosthetic mechanical valve in mitral position. He also had a left aortotomy performed, and underwent a Bentall procedure whereby a Carbomedics 23 valve conduit used. He had a smooth post-operative recovery, and discharged on oral anti-coagulant (Warfarin) with satisfactory International Normalization Ratio (INR). Two months after cardiac surgery the patient admitted to the neurosurgery department in a University Hospital for the repair of an Ethmoid sinus fistula, which he had sustained in the past RTA. He underwent all necessary pre-operative work and the operation was planned to take place 5 days after admission. However, one day before undergoing surgery he started to complain of progressive shortness of breath, orthopnea, Paroxysmal Nocturnal Dyspnea (PND) and exercise intolerance. Upon physical examination he looked ill, pale, and was in obvious respiratory distress and was unable to lie flat on the bed. His blood pressure was 95/65 mmHg, his pulse rate was 110 beats per minutes (bpm) and also showed signs of Atrial Fibrillation (AF). Moreover, his temperature was 36.8^{0}C, and his Respiratory Rate (RR) was 25 breath/minute. A chest examination revealed bilateral lung basal crepitation. The patient's Juguler Venous Pulse (JVP) was raised and he had significant bilateral lower limb pitting edema. A cardiac examination revealed the following; scar of median sternotomy non-displaced apex beat, reduced first heart sound (S1) and audible second heart sound (S2), audible valve click in the Aortic area which was not appreciated in the mitral area and furthermore no murmur was detected. A Complete Blood Count test (CBC), renal function test, serum electrolyte test (U&E), and Liver Function Test (LFTs) all produced results that were within the normal range. The coagulation profile revealed an Activated Partial Thromboplastin Time (APTT) of 49.4 seconds. Lastly, International Normalization Ratio (INR) test resulted in a value of 1.43.

A chest x-ray revealed signs of pulmonary edema, and bilateral small pleural effusion. Electrocardiography (ECG) demonstrated AF, with ventricular response rate of 131 beats per minutes (bpm). Moreover, Trans-Thoracic Echo-cardiography (TTE) revealed a large thrombus on the prosthetic mitral valve, thereby impairing the movement of the anterior mitral leaflet and restricting the diastolic filling of the left ventricle. This created a mean gradient of 23 mmHg on average (Figures 1 and 2).

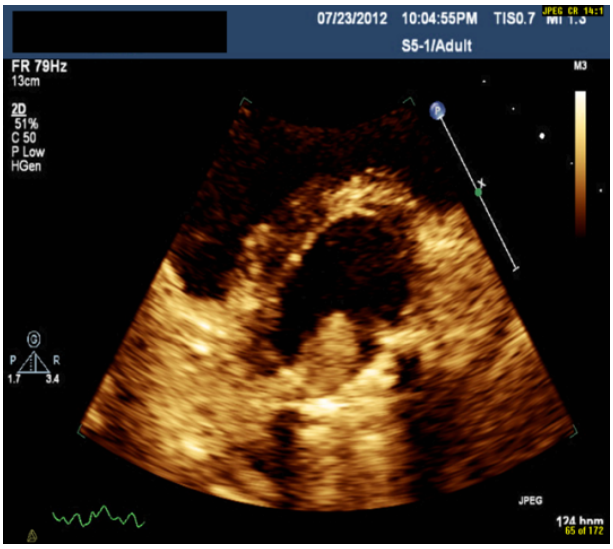

Figure 1: Two-dimensional Echo showing the section where the thrombus on the mitral metallic valve was prior to its removal.

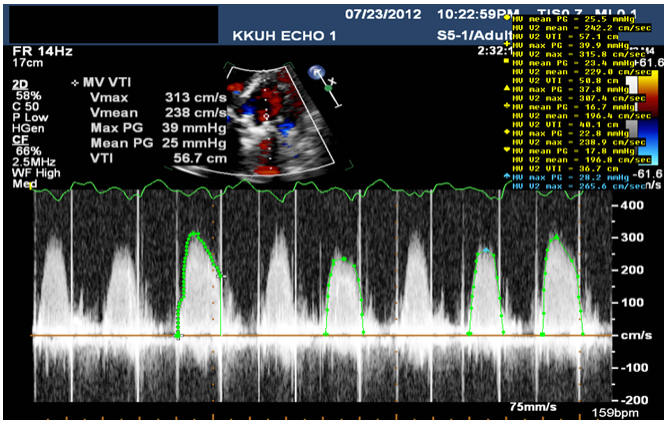

Figure 2: Shows the Doppler mean diastolic gradient of 23 mmHg across the metallic mitral valve.

The patient was diagnosed as having thrombosis of the mechanical mitral prosthesis and was transferred to the Coronary Care Unit (CCU). We started treatment for pulmonary edema and resumed anti-coagulation therapy with Unfractionated Heparin (UFH). Loading dose and continuous infusion to keep APTT in the range of 60-70 second and furosemide intravenous infusion. An urgent meeting took place between the heart team and the neuro-surgery team. where a detailed discussion led to the conclusion that this patient was at very high risk for re-do valve surgery which was immediately necessary especially in view of the status of the patient's brain condition and heart failure. The only viable treatment option was introduction of thrombolytic therapy despite there being a real risk for systemic embolization and bleeding. The patient and the patient's relatives were approached by the chief medics involved in the operation and the risk of disseminated thrombosis and bleeding were explained to them. Accordingly, their informed consent for thrombolytic therapy obtained. Besides heparin infusion, a t-PA of 15 mg was administered via Intravenous (IV) front-loading regimen which was followed afterwards by a 1 mg/hour IV infusion.

After 24 hours of t-PA infusion, the patient was still symptomatic with shortness of breath, orthopnea and PND. His blood pressure was 95/60mmHg, and pulse was 100 bpm in AF rhythm, with bilateral lung basal crepitation. Cardiac examination revealed reduced S1 intensity. Repeated TTE revealed a large residual thrombus with a reduced average mean diastolic gradient across the mitral prosthesis up to 8.0 mmHg (Figures 3 and 4).

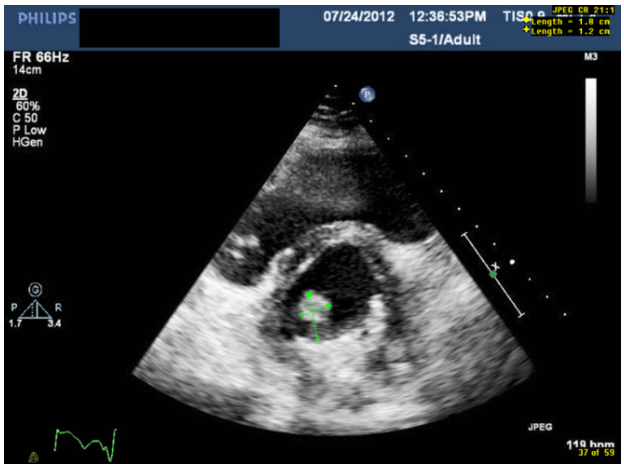

Figure 3: Shows a Two-dimensional Echo showing the reduced thrombus on the mitral metallic valve after 24 hours of treatment.

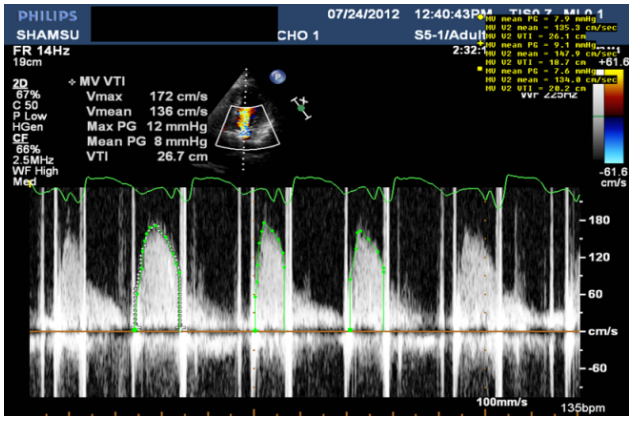

Figure 4: Shows the Doppler reduced mean diastolic gradient 24 hours after treatment started.

The t-PA infusion with the same rate of one mg per hour, in addition to the heparin IV infusion continued. After 48 hours of TPA infusion, the patient's symptoms improved, with spontaneous rhythm reversion from AF to sinus at heart rate 80 bpm, BP 120/80 mmHg. A chest examination revealed bilateral lung basal crepitation. The S1, and S2 were well heard, along with the metallic click of aortic and mitral valves, no murmur was detected. The patient reported two episodes of epistaxis in the last 24-hours, each episode lasting for a few minutes with minimal amounts of blood loss. This bleeding controlled by nasal packing during which the APTT was in therapeutic range, and reached a value of 79 seconds. An ECG confirmed a sinus rhythm, and a heart rate of 101 bpm. A TTE showed no residual thrombus on the mitral prosthesis and reduction of the diastolic gradient across the mitral prosthesis to 4.0 mmHg (Figures 5 and 6).

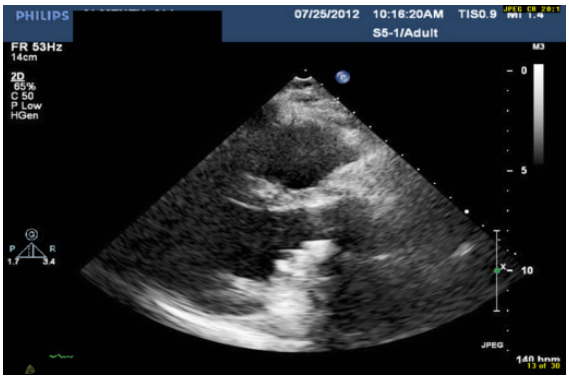

Figure 5: Shows a Twodimensional Echo revealing that there is no more thrombus on the mitral metallic valve by the end of the treatment.

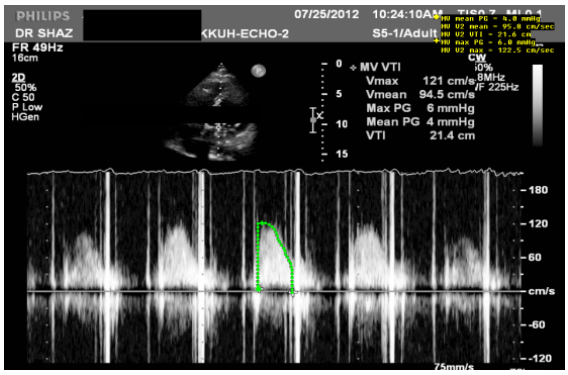

Figure 6: Shows a Doppler mean diastolic gradient of 4.0 mmHg, across the metallic mitral valve at the end of treatment.

Figure 5 shows a two dimensional Echo revealing that there is no more thrombus on the mitral metallic valve by the end of the treatment.

The clinical improvement and improved echocardiographic parameters indicated a successful response to t-PA. The total time of t-PA infusion was 57 hours. The administration of Heparin continued within the therapeutic range of 55-75 seconds. Oral Warfarin therapy started and the INR became therapeutic between 2.5 and 3.5. Warfarin therapy maintained on 6 mg at discharge.

DISCUSSION

Rheumatic valve diseases are the most frequently encountered type of valvular disease in developing countries and often require surgical replacement with prosthetic valves. However, Prosthetic Heart Valve Thrombosis (PVT) is a life-threatening complication whose management remains controversial. The management of PVT requires careful consideration as to whether a surgical or thrombolytic therapy should be carried out. There is, so far, no standardized first-line approach [11-14]. While surgical treatment is associated with increased mortality risk, the use of thrombolytics may cause bleeding, and cerebral embolization. The debate extends from being across single articles or reviews articles to debate of societies guideline and committees [15].

The American Heart Association and the American College of Cardiology recommend emergency surgery in unstable state like New York Heart Association (NYHA) class III-IV patients [11] These views are in contrast to the viewpoint of the American College of Chest Physicians who recommend fibrinolytic therapy for unstable NYHA III-IV patients [12]. However, according to the 2012, European Society of Cardiology and the European Association for Cardio-Thoracic Surgery guidelines, the management of left-sided Non-Obstructive Prosthetic Valve Thrombosis (NOPVT) depend mainly on the occurrence of a thromboembolic event and the size of the thrombus itself [13]. The European guidelines recommend surgery for large thrombi (≥ 10 mm). In NOPVT complicated by embolism (recommendation class IIa, level of evidence C) which persists despite optimal anticoagulation [13]. Fibrinolysis may be considered if the patient is at high risk as a result of surgical intervention. The American College of Chest Physicians (ACCP) recommends surgery for large thrombi and lytic therapy for small ones [16].

In 2014, the American guidelines state that [17] surgery recommended for patients in NYHA functional classes III and IV unless the surgery considered too high risk (class IIA).

The choice between medical or surgical management of prosthetic valve thrombosis, however, is not the only debatable issue as the optimal dose, frequency, and type of thrombolytic drug used have not been agreed upon so far. The study conducted by Loriga et al., used a regimen consisting of a loading dose of 250.000 units of Streptokinase over 30 minutes, then 100.000 units/hour over the next 72 hours with an overall success rate of 88%. Notably, 3% of patients suffered stroke but there was no mortality among low-risk stable patients .They also suggested the use of Urokinase 4400 units/kg as a loading dose in the first 30 minutes followed by 4400 units/kg/hour afterwards. It was not recommended in cases where patients reported a previous history of streptokinase use or had suffered an allergy after using streptokinase [18]. The research study

carried out by Manteiga et al., however, reported using a shorter but higher dose regimen of Streptokinase 1.500.000 units over ninety minutes administered as either one or two cycles with an overall success rate of 82%. Incidentally, only one patient suffered a stroke and another patient died during this trial. When Recombinant tissue-type plasminogen activator 100 mg was used over 90 minutes period, only 4 out of the 16 patients suffered a similar outcome to those in the aforementioned study. [19]. The use of recombinant tissue-type plasminogen activator is still less common than the use of Streptokinase for the treatment of prosthetic valve thrombosis [20] with two main regimens, the 100 mg loading dose over 90 minutes [2] versus the 1 mg/hour continuous infusion over 80 hours [21]. Those two methods have not been compared so far (Table 1).

Table 1: Summarizes the guideline recommendations in different clinical settings.

Guideline [reference]	Patient status	Treatment options
ESC 2012 [13]	Critically ill patients	Immediate surgery
	Severe comorbidities	Lytic treatment
	or unavailability or right-sided valves	-
	Non-obstructive PHVT if	-
	complicated by embolism or persists despite anticoagulation	Surgery
ACCP [16]	Left sided PHVT and large	Surgery
	thrombus area (≥ 0.8 cm^2)	-
	Left sided PHVT and	Lytic treatment
	small thrombus area (< 0.8 cm^2	-
ACC [17]	NYHA Class III, IV	Surgery
	Mobile or large clot	-
	burden (≥ 0.8 cm^2)	-
	Right sided valves	-
	NYHA Class I, II	Lytic treatment

The rationale behind the continuous low dose infusion is to avoid rapid lysis and reduce the rate of complications, while the reasoning behind a large brief loading dose with 100 mg t-PA over 90 minutes is to expedite the resolution of a clot and quickly restore any hemodynamic instability, if present, and prevent the risk of its progression further [21] . However, one study used the regimen of TPA 0.5 mg per kilogram body weight and 1.25 mg per hour infusion for 48 hours with successful results [22].

The TROIA study (2013) [23] evaluated a strategy of TEE-guided fibrinolysis. The patients included were 182 for 220 episodes of PVT. With rapid infusion of streptokinase (group I) versus slow infusion of streptokinase (group II) versus full-dose tissue plasminogen activator (t-PA) (100 mg) (group III) versus half dose (50 mg) slow infusion of t-PA (group IV) versus low dose (25 mg) slow infusion of t-PA (group V) . The study showed successful thrombolysis in 83.2% of cases without any significant difference between thrombolytic protocols. Significantly, though, this study showed that the reduced-dose protocol (25 mg of tPA infused over 6 hour) of thrombolytic treatment was effective with very low complications in patients with NOPVT and obstructive prosthetic valve thrombosis (OPVT). Table 2 below summarizes the different regimens of Tissue Plasminogen Activators (TPA).

Table 2: Summarizes the different regimens of Tissue Plasminogen Activators (TPA).

Reference [n]	Year	No. of Patients	Loading dose	Maintenance	Duration
Manteiga et al. [19]	1998	19	100 mg	non	90 minutes
Nguyen et al. [21]	2008	1	non	I mg / hour	80 hours
Al-Sarraf et al. [22]	2010	1	non	1.25 mg / hour	48 hours
Ozkan M et al. [23]	2013	182	100 mg	non	90 minutes
			non	50 mg	6 hours
			non	25 mg	6 hours
Ozkan et al. [24]	2015	114	non	25 mg	2 hours
Patil et al. [25]	2016	60	100 mg	non	3 hours
Our case	2018	1	15 mg	I mg/hour	57 hours

The patient who had previous intracerebral surgery post-RTA was faced with the dilemma of bleeding in the intra-cranial cavity when using thrombolytic therapy or the major risk of having re-do Valve surgery on an account of hemodynamic instability. The heart team and neuro-surgery team then reached a one-way decision regarding medical treatment whereby they opted to implement a novel regimen combining both of those treatment protocols via a small initial bolus dose and by maintaining a slow infusion dose afterwards. Therefore, the patient was loaded with 15 mg of r-TP-a followed by a 1 mg/hour infusion over the next 57 hours.

This unique protocol resulted in the elimination of thrombotic burden on the mitral metallic prosthesis and the restoration of hemodynamics. It also meant resolving the patient's symptoms without distant thrombo-embolization. The average mean diastolic gradient across the mitral prosthesis dropped from 23 mmHg before starting treatment to 8 mmHg after 24 hours of drug infusion followed by 48 hours of t-PA infusion after which time the mean diastolic gradient came down to 4 mmHg, which is the usual gradient in such mitral metallic prosthesis'. The initial plan had been to complete 72 hours of infusion–however, it was interrupted due to patient having two episodes of minor nasal bleeding which made us to stop the infusion at 57 hours. Until clear evidence emerges, the selective implementation of either regimen will remain the same based upon clinical sense and the expertise of the treating physician.

CONCLUSION

The occurrence of prosthetic valve thrombosis is rare but often results in serious complications pertaining to valve replacement. The available treatments up to the present time are, 1) Redo surgery, or, 2) Thrombolytic therapy. The decision to select either strategy depends upon multiple factors such as the patient's medical condition, the expertise of the cardiac surgeon involved and the multidisciplinary team agreement of various issues. There is a current lack of randomized controlled prospective trials comparing surgical and thrombolytic therapies. Further research is necessary in order to amalgamate all previous related data and come up with new unified guidelines for the management of mechanical valve thrombosis. The patient featured in this study was a high-

risk patient as he was in NYHA class IV. Considering that he had atrial fibrillation and post brain surgery, he still showed miraculous recovery after the 15 mg IV bolus of t-PA followed by a 1 mg/hour infusion for 57 hours. Until a common consensus or further studies establish the exact approach needed for the treatment of such a condition, we recommend considering the same regimen as described in this paper when the patient's condition is unstable. It is noteworthy however, that such treatment may carry a high risk of thrombolytic complications for the patient.

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