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Thrombolysis in high-risk patients with left-sided obstructive prosthetic valve thrombosis

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INTRODUCTION

Prosthetic Valve Thrombosis (PVT) is one of the most dreaded complications of mechanical heart valves. The incidence of PVT is estimated at 0.3% to 1.3% per patient year in developed countries, but as high as 6.1% within 6 months of valve replacement in developing countries.[1,2] In a recent study of new generation bioprosthetic surgical aortic valve, thromboembolic event rate was 2.3% within 30 days.[3] Published guidelines differ over the best line of therapy for PVT; The European Society of Cardiology (ESC) valve guidelines recommend surgery as a Class I treatment for obstructive PVT (OPVT) in critically ill patients without serious comorbidity and to consider standard dose thrombolytic therapy (TT) when surgery is not available or deemed high risk- (class IIa recommendation), while the American College of Cardiology (ACC)/American Heart Association (AHA) 2017 focussed update recommends urgent initial treatment with either slow infusion, low dose TT or emergency surgery (class I) for OPVT.[4,5] We aimed to evaluate the clinical profile, management strategies and outcome of patients presenting with left sided mechanical OPVT.

METHODS

We included patients admitted with mechanical OPVT to our institute between July 2014 and July 2019. Our centre is a tertiary referral institute with capability of emergency valve surgery. PVT was confirmed based on clinical presentation, transthoracic echocardiography (TTE) and fluoroscopy findings. Patients with infective endocarditis and non-obstructive PVT were excluded from the study. We defined subtherapeutic International Normalised Ratio (INR) as ≤ 2 in aortic and ≤ 2.5 in mitral mechanical valve patients.

The dose and choice of TT (streptokinase/ Tenecteplase/ Alteplase) were at the discretion of the treating cardiologist. TT was considered to be successful, if there was 50%

reduction in transvalvular gradient on TTE with clinical improvement in the absence of death or need for surgery.

Categorical variables are expressed as numbers and percentages and continuous variables are expressed as mean (SD), unless mentioned otherwise. Comparison of categorical variables was done by Fisher's exact test and comparison of continuous variables was done either by *t*-test (both paired and unpaired) or Mann-Whitney U test based on the normality of the data. Data analysis was carried out by SPSS v25.0. All 'p' values <0.05 were considered as statistically significant. The study was conducted in compliance with the ethical standards of the responsible institution as well as with the 1975 Declaration of Helsinki.

RESULTS AND DISCUSSION

A total of 46 patients [50 (12) years, 19 female] were included in our study. Aortic OPVT is predominant with 27 patients (59%), mitral OPVT in 18 (39%), while one patient had both valves involved (2%). Valve design was mostly bileaflet (65.2%), with tilting disc in 30.4% and ball and cage model in 4.4% of patients. The duration between surgery and this OPVT episode was significantly shorter in the mitral compared to aortic OPVT [49, 20-83 vs 78, 38-145 months, (median, IQR), $P = 0.04$]. The mean pressure gradient (MPG) was 71 (26) mmHg and 25 (7) mmHg in aortic and mitral OPVT respectively. The admission INR was 2.02 (0.6), while 35 (76%) had subtherapeutic levels. (Table S1)

Out of the 44 patients who had TT (Streptokinase- 27%, Tenecteplase- 32% and Alteplase - 41%), five were unsuccessful (4 aortic/1 mitral) (Figure 1). In those who had successful TT (89%), the post-lysis echo showed mean MPG of 31.3 (24.5) mmHg in aortic [pre-lysis 71 (26) mmHg, $P < 0.0001$] and 9 (4) mmHg [pre-lysis 25 (7) mmHg, $P <0.0001$] in mitral OPVT. (Figure S2)

Six of the 46 patients (13%) died during hospital stay including the one who underwent surgery without TT. Three patients (7%) had intracranial hemorrhage and 2 patients (4%) had ischemic stroke. One another patient (2%) had gastric bleed requiring blood transfusion. The in-hospital mortality (IHM) rate of patients who had TT in our study was 4/44 (9.1%). During a median follow up period of 21 (IQR 10-44) months, 3 patients died (3/40, 7.5%) and 2 had undergone redo-valve surgery due to recurrent OPVT (2/40, 5%). The overall mortality rate of all OPVT patients included in the study was 19.6% (9/46), while in thrombolysed patients it was 15.9% (7/44).

Our study has few unique findings when compared to some of the previous observational reports. Firstly, our study had more aortic OPVT compared to mitral OPVT. This could partly be explained by the fact that our study included only obstructive PVT; patients with mitral OPVT might not have survived to reach hospital, whereas patients with aortic OPVT tolerated it better. Most previous studies included both obstructive and non-obstructive PVT; like the PRO-TEE registry, TROIA and PROMETEE studies had 15%, 50% and 36% of non-obstructive PVT respectively.[6-8] This could be the reason for higher mitral PVT included in those studies. On a similar note, there was one study looking only at non-obstructive PVT had 97% mitral involvement in their series.[9]

There were three important meta-analysis/systematic reviews related to the management of PVT comparing TT versus surgery, from which the European and American guidelines were derived. Two of these meta-analysis did not differentiate obstructive and non-obstructive PVT patients in their analysis.[10-11] The only systematic review by Huang et al, mentioned specifically looking at OPVT included a literature survey of 17 studies comprising 756 patients who had received TT and 13 studies comprising 662 patients who had received surgery for OPVT.[12] This showed a 30-day mortality rate of 8% vs 15% in TT vs Surgery and the recurrence rate was higher (13%) in thrombolysis group. On this basis,

the authors recommended thrombolysis as a first choice for patients in NYHA Class I/II with severe co-morbid conditions associated with a high surgical operative mortality and recommended surgery as the preferred therapy for patients in NYHA class III/IV and with a large thrombus (area ≥ 0.8 cm2). In this analysis, only 65% of the thrombolysis patients were in NYHA class lll/ IV and their success rate was only 74% compared to 81% in NYHA class I/II patients.[12]

Naturally, due to the inclusion of only obstructive PVT, our study included more patients (85%) with NYHA class III/IV symptoms and our thrombolysis success rate in this group was 87%. The other studies which included both non-obstructive and OPVT had comparatively lower number of patients with NYHA class III/IV symptoms, for eg. TROIA and PROMETEE study had 41% and 36% patients respectively. Despite our study population being considered high risk, the mortality rate of patients who underwent thrombolysis (9.1%) were similar to the previous available data of around 8-9%.

One another strength of our study is the longer follow up period with a median of 21 (IQR 10-44) months, as most previous studies had 30-day outcome data. The recurrence rate was low at 5% in our study, whereas in the systematic review the recurrence rate of OPVT in patients who had thrombolysis was 13% with no clear time frame mentioned.[12]

Our study is a single centre observational analysis, with its inherent limitation of a retrospective study. Only the dose of streptokinase was followed uniformly- 250,000 IU bolus followed by 100,000 IU/hour infusion, while the dose of Tenecteplase and Alteplase used were different among the treating cardiologists. Trans-esophageal echocardiogram (TEE) was not performed routinely for all OPVT patients in our unit and therefore the data is unavailable.

In conclusion, our study shows that even in high risk patients with mechanical OPVT, thrombolysis is beneficial with 89% success rate and 5% recurrence rate despite a longer

follow-up period. In OPVT, a randomized prospective multicentre study is needed to provide evidence of superiority and safety of thrombolysis over surgery, and to identify those patients who benefit the most from thrombolysis.

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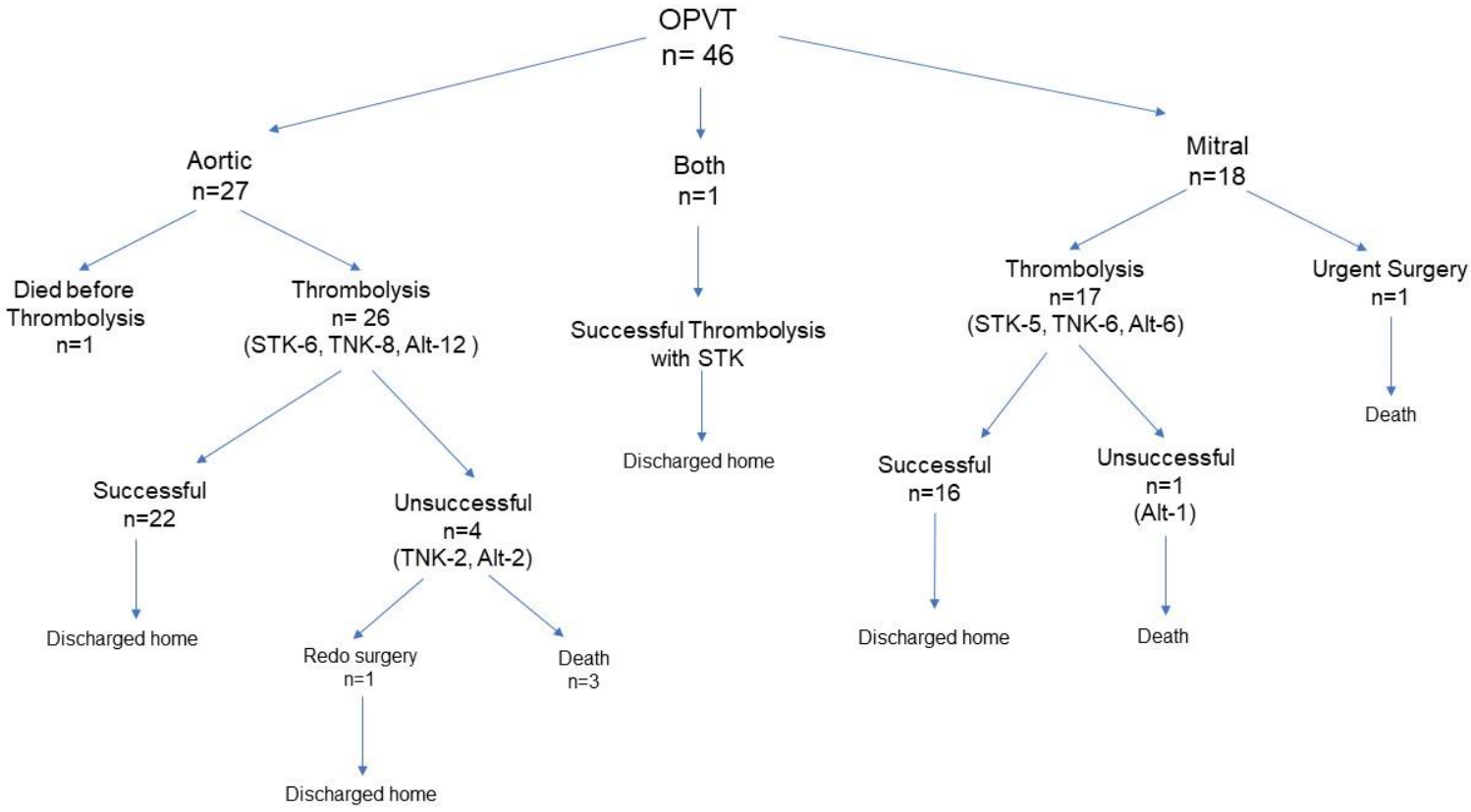

Figure 1. Flow chart of management of patients admitted with Obstructive Prosthetic Valve Thrombosis.

Footnotes- STK- streptokinase, TNK- Tenecteplase, Alt- Alteplase