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Two and real-time three dimensional transesophageal echocardiography guided thrombolytic therapy for prosthetic valve thrombosis is crucial

To the Editor,

We have read with great interest the article by Kathirvel et al which was recently published in the Indian Heart Journal.[1] We commend the authors for this important report describing clinical outcomes with tenecteplase (TNK) versus streptokinase thrombolytic therapy (TT) in patients with mitral prosthetic valve thrombosis (PVT). However, at the same time, we would like to highlight some important issues that need to be addressed.

First, TNK, a tissue-type plasminogen activator modified by 3 amino acids from alteplase, has the potential to deliver this kind of performance. It has greater fibrin specificity resulting in no evidence of systemic fibrinogen depletion and resistance to plasminogen activator inhibitor resulting in an initial serum half-life of 20 min and a mean terminal half-life of 100 min, such that it can be conveniently given as a bolus dose (over 5 s) on a weight-adjusted basis. At a dose of 0.5 mg/kg, it has been a standard of care for treating acute ST-segment elevation myocardial infarction for 15 years.[2] In this study, 12 of the 52 patients with PVT were treated with a 24-h infusion of TNK. According to the manufacturer's guidelines, the reconstituted solution should be diluted with sterile water for injection up to a maximal concentration of 5 mg TNK per ml, and it should be administered as an intravenous single bolus dose over 5 s. The remaining TNK solution, if needed, may be kept in the vial for up to 8 h, but at 2–8 °C temperature.[3] How were the biological stability and efficiency of reconstituted solution ensured during the 24-h infusion?

Second, transthoracic echocardiography (TTE) usually offers inadequate images in making differential diagnosis of thrombus, pannus, and vegetation due to acoustic shadowing and low resolution caused by prosthetic material. On the other hand, transesophageal echocardiography (TEE) with its high resolution may differentiate thrombus from pannus formation and vegetation in patients with PVT. Furthermore, TEE is also of great value with regard to the assessment of mobility, location, and thrombus size; this may assist in the decision regarding surgery, anticoagulation, or TT. In addition, a large residual nonobstructive PVT may be present in some patients who have experienced successful TT, but it may be missed during TTE study. The detection of nonobstructive PVT can be challenging, particularly when Doppler parameters are within normal limits and clinical findings are subtle. Hence, nonobstructive PVT can even be missed with conventional 2D imaging. In comparison, real-time three-dimensional (RT-3D) TEE, over the last decade, has emerged as an important clinical tool in the assessment of PVT. RT-3D TEE has higher spatial resolution, resulting in images with unparalleled anatomic detail when compared with 2D imaging. The diagnostic accuracy for detecting PVT has improved after the introduction of RT-3D TEE, especially for those in mitral position [4–6]. It is understood that cine fluoroscopy is effective at detecting abnormality of leaflet mobility, and TTE may provide data regarding changes in valve area and transvalvular gradients. Nevertheless, these imaging tools are complementary to TEE, which offers a fundamental roadmap for TT in patients with PVT.

Third, patients with thrombus with size >1 cm^2 were included in the trial. It is surprising why these patients were not given TT and were excluded from the trial. İt is noteworthy that the recent 2017 American Heart Association (AHA)/American College Cardiology (ACC) focused update of the 2014 AHA/ACC guideline for the management of patients with valvular heart disease now recommends urgent initial treatment with either slow-infusion low-dose fibrinolytic therapy or emergency surgery for obstructive PVT as first-line treatment strategies with class 1-B indication.[7]

In conclusion, during TT in patients with PVT, continuous TEE guidance is crucial. Moreover, RT-3D TEE is a complementary imaging tool to 2D TEE in the diagnosis and evaluation of PVT. Finally, if TEE had been performed on all the patients in the study both before and after TT, the unexpected results would not have been the same.

Conflict of interest

The authors declare that they have no conflict of interest.

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Authors' response to "Letter to Editor"

We thank the authors of the letter for their interest in our work and for making valid observations. Please find below our responses.

Biological stability of tenecteplase during continuous infusion.

There are not many studies on the use of tenecteplase (TNK) in the management of prosthetic valve thrombosis (PVT), and we do not have clear guidelines for the same. Few earlier case reports have documented the use of continuous infusion of TNK in PVT[1,2] and peripheral arterial thrombosis.[3] Total dose of 0.5 mg/kg of TNK was used as a continuous infusion in cases of PVT, whereas in acute limb ischemia, 0.25–0.5 mg/h of TNK was used with a mean infusion time of 7.5 h (range, 3–20 h). The mode of administration and optimal dose of TNK in the management of PVT are still evolving. As per the manufacturer's guidelines, the shelf life of reconstituted solution (maintaining physical and chemical stability) is at least 8 h when maintained at a temperature less than 30 °C and 24 h when maintained below 8 °C. The previously cited studies have documented efficacy of TNK infusions continued over durations longer than 8 h. We also observed the clinical efficacy of TNK in reducing the gradients and improving the clinical status after 8 h of infusion in 7 of our patients.

We would also like to emphasize that unlike acute myocardial infarction, where the time is muscle and lytic therapy has to be administered as fast as possible, with PVT, there is a longer thrombolytic window. Moreover, we felt that the larger burden of thrombus with PVT necessitated a slower infusion over a longer period.

Use of transesophageal echocardiography and real-time three-dimensional transesophageal echocardiography in diagnosing PVT

Although transesophageal echocardiography (TEE) seems to be ideal, we could obtain reasonably good images with transthoracic echocardiography (TTE) in most of our patients. We used TEE and fluoroscopy as an additional tool whenever TTE images were deemed to be inadequate.

We also agree that real-time three-dimensional (RT-3D) TEE can improve diagnosis of PVT. However, with the appropriate clinical picture, the use of TTE, and whenever needed TEE and fluoroscopy, the diagnosis of PVT could me made with certainty in all our cases.

Patients with thrombus size >1 cm^2 were excluded from this study

We had started this study in 2014, when the recommendation for PVT with thrombus size >0.8 cm^2 was emergency surgery (class IIa indication). Hence, the patients with thrombus size more than 10 mm^2 were not included in this study that aimed to evaluate the role of thrombolytic therapy in PVT.

However, we wish to inform the readers that this study was a part of the ongoing Madras Medical College PVT registry. Subsequent to the publication of the 2017 American Heart Association (AHA)/American College of Cardiology (ACC) focused update of the 2014 AHA/ACC guideline for the management of patients with valvular heart disease, now the patients with thrombus size more than 10 mm^2 are also being considered for thrombolytic therapy at our center.

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Further reading

4. Table 2 of our research article, Kathirvel D, Justin Paul G, Prathap Kumar G, et al. Tenecteplase versus streptokinase thrombolytic therapy in patients with mitral prosthetic valvethrombosis. *Indian Heart J*. 2018 Jul–Aug;70(4):506–510.

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