Archives of Current Medical Research
Arch Curr Med Res 2022;3(2):120-125

Received: 16 February 2022
Revised: 21 April 2022
Acccepted: 19 May 2022
DOI: 10.47482/acmr.2022.56

ORIGINAL ARTICLE

Outpatient use of tPA to recanalize thrombosed native fistulas a case series and discussion of literature

Işıl Yıldız[1], **Demet Gündüz**[2], **Can Çalışkan**[1],

1 Acibadem University Atakent Hospital, Department of Radiology, İstanbul, Turkey
2 Süleyman Demirel University Faculty of Medicine, Department of Radiology, Isparta, Turkey

Abstract

Background: The present study aims to evaluate the effectiveness of ultrasound-guided percutaneous alteplase (t-PA) injection for the treatment of long segment (≥14cm) thrombi in the efferent veins of native arteriovenous fistulas in hemodialysis patients.

Methods: A total of 9 patients who underwent t-PA application under ultrasound guidance in the interventional radiology clinic between 2019 and 2021 were included in the study. During the intervention, information such as thrombosed segment length, t-PA dose, number of sessions, presence of aneurysmal segment, bleeding after the intervention and the need for percutaneous transluminal angioplasty (PTA) were recorded. Restoring the flow in the fistula was considered the successful outcome. All statistical evaluations were performed with the IBM SPSS Statistics 21 software (version 21.0; SPSS Inc, Chicago, Illinois) for Windows.

Results: Mean age of the patients was 48.7±14 years, the fistula age was 28.7±11 months, the thrombosis age was 3.5±2 days, and the thrombosed segment length was 17.7±2.9 cm. Post-intervention bleeding that did not require treatment was encountered in 2 patients, and stenosis in the proximal fistula was encountered in 6 patients. PTA was applied to 7 patients after t-PA. After the interventions, effective flow was provided in all patients.

Conclusion: Ultrasound-guided percutaneous t-PA injection should be considered as an effective intervention which is less invasive, can be performed as an outpatient intervention and has fewer complications, even if the thrombi segments are long (>10 cm). This technique avoids the potential endothelial damage and saves the cost of the mechanical devices.

Keywords: Hemodialysis, Thrombosis, Tissue Plasminogen Activator.

Cite this article as: *Yıldız I, Ünal D, Çalışkan C. Outpatient use of tPA to recanalize thrombosed native fistulas a case series and discussion of literature Arch Curr Med Res. 2022;3(2):120-125*

Corresponding Author:
Işıl Yıldız, Acibadem University Atakent Hospital,
Department of Radiology, İstanbul, Turkey
E-mail: drisilyildiz@gmail.com

INTRODUCTION

Arteriovenous (AV) fistula, AV graft and tunneled hemodialysis catheters are used for hemodialysis applications (1,2). Complications such as venous aneurysm, infection, skin necrosis, steal syndrome, thrombosis and stenosis are encountered in patients who undergo arteriovenous fistula applications (3). The National Kidney Foundation Disease Outcomes Quality Initiative recommends that fistulas be preferred over grafts, as they have lower complication rates (4). However, thrombosis is a common complication of AV fistulas. Intimal rupture in the fistula triggers thrombocyte aggregation and causes thrombosis (5). Methods such as surgical thrombectomy, thromboaspiration and thrombolytic agents like t-PA are used in treatment (6, 7).

Plasmin is an enzyme that has a thrombolytic effect by breaking the cross-links between fibrin molecules in thrombus content. t-PA is involved in the formation of plasmin from plasminogen. It is used as a thrombolytic agent in the treatment of various diseases (8-10). Ischemic stroke, myocardial infarction, pulmonary embolism, and deep vein thrombosis are the main indications for these drugs (8, 9, 11). The main types of t-PA are alteplase, reteplase and tenecteplase. Nowadays, recombinant tissue plasminogen activator(rt-PA) can be produced in the laboratory. It has been approved by the US Food and Drug Administration (FDA) for use in cases of thrombosis, especially in alteplase central venous access catheters (12). Each vial of alteplase contains 10, 20 or 50 mg rt-PA. The reconstituted solution contains 1 mg alteplase per mL.

There are studies in the literature regarding the use of t-PA for thrombosis in both AV fistula and grafts in patients, who underwent hemodialysis due to chronic renal failure. As it is minimally invasive, t-PA is administered as a bolus from catheters placed in the fistula vein, by slow infusion via infusion catheters or by percutaneous injection directly into the graft (13-16). In this study, we aimed to evaluate the results of ultrasound-guided percutaneous t-PA injection in thrombosed native veins for the treatment of long segment thrombi in the efferent vein of the arteriovenous fistula.

MATERIALS AND METHODS

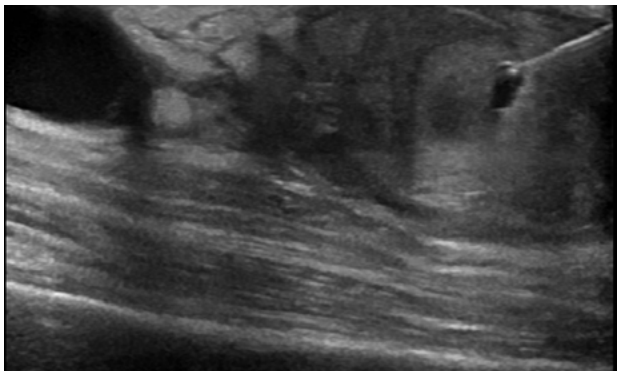
Patients who were treated with the diagnosis of dysfunction due to long segment thrombosis in hemodialysis fistula and who were admitted to our hospital's interventional radiology clinic between 2019 and 2021 were retrospectively reviewed. All patients who received percutaneous t-PA injections were included in the study. In our clinic, the diagnosis of thrombosis is made with ultrasonography (USG) by observing the thrombus in the fistula. Those with short segment thrombosis are treated with for thromboaspiration and if necessary balloon angioplasty is performed. We did not include these patients to our study.

Patients with t-PA contraindications, such as head trauma or stroke suffered in the previous three months, subarachnoid hemorrhage symptoms, a history of intracranial hemorrhage, a history of arterial interference in the previous seven days and intracranial neoplasia were not included in the study. Apart from these, the patients who did not attend the control appointments (n = 2) were excluded from the study. The remaining 9 patients (6 men and 3 women) were included in the study. Demographic data and clinical examination findings of the patients were obtained from the patient registry system. In addition, information on fistula duration, thrombosis duration, thrombosed segment length, fistula type, applied t-PA dose, number of sessions, presence of aneurysmal segment, bleeding after the intervention and the need for percutaneous transluminal angioplasty (PTA) after thrombolysis were obtained from the hospital records (Table 1). Informed consent forms were obtained from all patients before treatment.

Technique: In the study, alteplase injections to efferent veins in AV fistulas were performed percutaneously with USG guidance. All AV fistulas had dysfunction due to occlusion. This intervention was applied in the outpatient clinic of interventional radiology department. For the intervention sterile field preparation in the supine position was done; 27-gauge (G) needle and a 20cc syringes were used (Fig 1). No local anesthetic or prophylactic antibiotics were administered. 5-8 mg alteplase was completed up to 20 cc with physiological saline was used per session. 1-2 cc of the alteplase-saline mixture was injected into the thrombus with 2-2.5cm intervals with USG (Logic S8, GE (New York, USA)) guidance. The sessions were repeated until no thrombus remained in the vein. Low molecular weight heparin (enoxaparin sodium) was prescribed at therapeutic dose. First dose was administered at the

hospital after the intervention Patients were followed up in the hospital for 2 hours after the intervention for observation. During discharge, patients were warned about not using their upper extremity with the AV fistula to prevent bleeding.

Figure 1: Injection of TPA into the thrombus



On the second day after the intervention, patients were called out to outpatient clinic. If residual thrombus was detected with US the intervention was repeated in the same fashion. After the second intervention fistulas were checked with USG on the day after. PTA was performed on the day when no thrombus found on USG examination. During the period from first injection until PTA, enoxaparin sodium was administered at the therapeutic dose. Flow volume of >600 ml/min, and a full dialysis session through reopened fistula considered to be successful treatment.

Statistical method writing : Quantitative variables are presented as mean ± SD (standard deviation) in tables and median (minimum / maximum), while categorical variables are shown as n (%).

This study was approved by the clinical research ethics committee of the Acıbadem University (Date: 28.01.2022 number: 2022-02/08).

RESULTS

9 patients with a mean age of 48.7 ± 14 (min: 32- max: 72) were included in the study. The mean age of fistula was 28.7 ± 11 months, that of thrombosis was 3.5 ± 2 days, and the length of the thrombosed segment was 17.7 ± 2.9 cm. Fistula types, t-PA dosage, and number of applications are shown in Table 1.

Aneurysmal segment was observed in three patients. In two patients, bleeding occurred at the needle insertion sites within the first 24 hours after the intervention which is controlled with compression. Hospitalization, additional intervention or erythrocyte replacement was not required for these patients.

Six of the patients included in the study had stenosis (4 subclavian, 1 brachiocephalic, and 1 vena cava superior). Two patients did not have any stenotic segment. Severe hypotension caused thrombosis in these patients. If present, stenoses were treated with PTA which is a very short procedure after thrombus disappeared (2nd or 3rd day of the treatment). All patients were able to have hemodialysis via AVFs at maximum 3 days after the first injection of t-PA. The therapeutic dose of enoxaparin sodium was continued until PTA was administered. Patients, who underwent PTA, continued to receive therapeutic dose of enoxaparin sodium for one more week and maintenance dose for the next 3 weeks. One patient who underwent percutaneous t-PA injection and PTA due to central vein stenosis presented with recurrence of fistula dysfunction in the 3rd month after the treatment. There were no thrombi that's why PTA was performed due to restenosis of the central vein. Another patient who did not use enoxaparin sodium regularly was admitted to the outpatient clinic with occlusion due to rethrombosis 17 days after the treatment. t-PA was applied by using the same protocol but this time intervention was not successful. The fistula was recanalized with endovascular thrombectomy and PTA. We assume that our technique was unsuccessful because of the old age of the thrombi.

DISCUSSION

Surgical thrombectomy and endovascular interventions are used in the treatment of thrombosis. In the study published by Marston *et al*. in 1997, surgical thrombectomy was shown to be superior to endovascular interventions, but urokinase was used as a thrombolytic agent in this study (10). After recombinant t-PA (r-tPA) is produced in the laboratories, urokinase was not the preferred thrombolytic agent anymore because studies showed that thrombolysis with r-tPA is more successful than surgical thrombectomy. (7,18,19,20,21).

In a systematic review conducted in 2011, three different r-tPA agents were compared with each other and it was

shown that the success rate was 88% with reteplase, 81% with alteplase, and 41% with tenecteplase (22). In our study, we used alteplase, which has been proven to be effective.

In addition, an advantage of endovascular interventions is that the underlying stenosis can also be treated in the same session (23). In our study, successful results were obtained as a result of USG-guided t-PA injection. Effective hemodialysis was possible after treatment in all patients. PTA was applied for stenoses (n = 7) after t-PA. Because no treatment for thrombus is needed during the angiographic intervention, only PTA is performed in the angiography room.

Thrombi older than two weeks are considered chronic (24,25). Because fibrin crosslinks change after two weeks and tPA actively degrades fibrin crosslinks, chronic thrombi are resistant to thrombolytic therapies and anticoagulation (26-28). We assume that this was the reason of the failed procedure of the patient with rethrombosis. The thrombus was chronic (17 days old).

Acute thrombi age and infusion time of t-PA are other issues. In a study in which 42 thrombosed fistulas were included, no significant correlation was found between the younger thrombus age and the success of the treatment. In our study, patients applied to us after the fistula was occluded. We considered the time elapsed from the time the fistula stopped to the time we performed the intervention as the age of thrombus. Based on this assumption the thrombi age in our study is younger than 7 days. However, even if thrombus fragments of different ages are considered in such a long segment thrombus, it was thought that no fragment was older than 15 days, based on the effectiveness of t-PA (29).

In the study conducted by Regus et al. (30) in 2017, patients were divided into two groups as short (<3 hours) and long (≥3 hours) infusion times. It has been shown that a longer infusion time provides a more effective thrombolysis and causes fewer complications in the long term. In this study r-TPA dose ranges 2-6mg which is lower than ours. But the success rates are 85.7% and 89.7% . Unlike these studies short-term application was found to be effective in our study. However, there was no comparison group who received infusion over a longer period. In addition, we think that the factor that makes it effective, despite its short duration, may be the method of administration. In this study, thrombolytic injection was performed directly into the thrombus accompanied by USG without using infusion catheter or angiography guidance. Similarly, in the study of Durmaz et al. (13), 5-10 mg t-PA was administered as a single injection directly into the thrombus and 100% success was achieved. According to that study, successful results were obtained although the lengths of thrombosed segments of the patients included in our study were longer. In the aforementioned studies, a total dose of 2-2.5 mg was administered. In our study, a total dose of 5-8 mg t-PA was administered directly into the thrombus within approximately five minutes. It is not possible to compare the studies with each other due to different application techniques.

Dose of the t-PA administered for AVF thrombosis is variable. Schon et al. (14) studied on reducing the t-PA dose the reduced dose found successful ranged between 0.5-7.5mg for thrombus length of 0.5cm to more than 10cm. Our doses range is 5-8 mg for thrombus longer than 10cm meaning r-tPA doses for long thrombus is similar.

In their study in 2011, Chang et al. (31) showed that low-dose t-PA administered directly into the thrombus once a day was at least as effective as thrombolytic infusion treatment with a catheter in deep vein thrombosis the application that corresponds most closely to the method employed in our study was made in a retrospective study of Durmaz et al. (13) in 2019. Nearly complete success was achieved in the study in which 17 patients were included and t-PA injection was performed in the native hemodialysis fistula under the guidance of USG. Unlike this study, the duration of thrombosis was less than 2 weeks in all patients included in our study, and the thrombosed segment length was over 10 cm in all patients. When compared with the study of Durmaz et al. (13), we conclude that success can be achieved in acute thrombi, even if the thrombosed segment is over 10 cm. The most important difference in the method used in this study from other studies in the literature is that successful results were obtained in long segment thrombi.

There is a need for a large series of prospective randomized studies consisting of standard groups on this subject. We think that it is a more economical method

compared to the methods used in other studies because it is not an angiographic intervention and it is a method that is more adaptable for the patient because it does not require hospitalization.

This study has some limitations. The method employed was applied to patients who were not suitable for surgical thrombectomy and who did not want to be hospitalized and therefore could not have an infusion catheter, and it was observed that a successful result was obtained. The study was designed retrospectively based on this observation. Due to the retrospective study design, patient selection, standard patient groups and randomization could not be made. The limited number of samples was also a limitation in the interpretation of the data obtained. Although patient age and fistula age spread over a wide range create limitations in evaluating the results, the presence of acute thrombus in all patients, similar thrombosed segment length and standard dose and duration of t-PA are strengths of the study. The most important difference in this study is that the method was applied in long segment (>10 cm) thrombi and achieved successful results, especially when compared with studies in the literature. This is the first study done on such long segment thrombi.

In conclusion, ultrasound-guided t-PA injection should be considered as it is a less invasive, effective intervention that can be performed without hospitalization and has fewer complications, even if the thrombi are long segments (>10 cm) that develop in patients with native AV hemodialysis fistula. This technique avoids the potential endothelial damage and cost of the mechanical devices. Moreover, it is a time saving intervention for the interventional radiologists, helps to reduce the x-ray exposure by shortening the time spend in the angiography unit.

Declarations

The authors received no financial support for the research and/or authorship of this article. There is no conflict of interest.

This study was approved by the clinical research ethics committee of the Acıbadem University (Date: 28.01.2022 number: 2022-02/08).

REFERENCES

1. Agarwal AK, Haddad N, Boubes K. Avoiding problems in tunneled dialysis catheter placement. Semin Dial 2019; 32(6):535-40.
2. Murea M, Geary RL, Davis RP, Moossavi S. Vascular access for hemodialysis: A perpetual challenge. Semin Dial 2019; 32(6):527-34.
3. Al-Jaishi AA, Liu AR, Lok CE, Zhang JC, Moist LM. Complications of the Arteriovenous Fistula: A Systematic Review. J Am Soc Nephrol 2017; 28(6):1839-50.
4. Coleman CI, Tuttle LA, Teevan C, Baker WL, White CM, Reinhart KM. Antiplatelet agents for the prevention of arteriovenous fistula and graft thrombosis: a meta analysis. Int J Clin Pract 2010; 64(9): 1239-44.
5. Swedberg SH, Brown BG, Sigley R, Wight TN, Gordon D, Nicholls SC. Intimal fibromuscular hyperplasia at the venous anastomosis of PTFE grafts in hemodialysis patients. Clinical, immunocytochemical, light and electron microscopic assessment. Circulation 1989; 80(6): 1726-36.
6. Dougherty MJ, Calligaro KD, Schindler N, Raviola CA, Ntoso A. Endovascular versus surgical treatment for thrombosed hemodialysis grafts: A prospective, randomized study. J Vasc Surg 1999; 30(6):1016-23.
7. Marston WA, Criado E, Jaques PF, Mauro MA, Burnham SJ, Keagy BA. Prospective randomized comparison of surgical versus endovascular management of thrombosed dialysis access grafts. J Vasc Surg 1997; 26(3):373-80; discussion 80-1.
8. Gravanis I, Tsirka SE. Tissue-type plasminogen activator as a therapeutic target in stroke. Expert Opin Ther Targets 2008; 12(2):159-70.
9. Heiferman DM, Li DD, Pecoraro NC, Smolenski AM, Tsimpas A, Ashley WW Jr. Intra-Arterial Alteplase Thrombolysis during Mechanical Thrombectomy for Acute Ischemic Stroke. J Stroke Cerebrovasc Dis 2017; 26(12):3004-8.
10. Islam MS. Thrombolytic Therapy by Tissue Plasminogen Activator for Pulmonary Embolism. Adv Exp Med Biol 2017; 906:67-74.
11. Sharifi M, Bay C, Nowroozi S, Bentz S, Valeros G, Memari S. Catheter-directed thrombolysis with argatroban and tPA for massive iliac and femoropopliteal vein thrombosis. Cardiovasc Intervent Radiol 2013; 36(6):1586-90.
12. Demaerschalk BM, Kleindorfer DO, Adeoye OM, Demchuk AM, Fugate JE, Grotta J et al. American Heart Association Stroke Council and Council on Epidemiology and Prevention. Scientific Rationale for the Inclusion and Exclusion Criteria for Intravenous Alteplase in Acute Ischemic Stroke: A Statement for Healthcare Professionals From the American Heart Association/American Stroke Association. Stroke. 2016;47(2):581-641.
13. Durmaz H, Birgi E. A promising method for the salvage of thrombosed native hemodialysis fistulas: percutaneous ultrasound-guided thrombolytic injection. Turk J Med Sci 2019; 49(4):1179-84.
14. Schon D, Mischler R. Salvage of occluded autologous arteriovenous fistulae. Am J Kidney Dis. 2000; 36(4):804-10.
15. Falk A, Mitty H, Guller J, Teodorescu V, Uribarri J, Vassalotti J. Thrombolysis of clotted hemodialysis grafts with tissue-type plasminogen activator. J Vasc Interv Radiol 2001; 12(3):305-11.
16. Vogel PM, Bansal V, Marshall MW. Thrombosed hemodialysis grafts: lyse and wait with tissue plasminogen activator or urokinase compared to mechanical thrombolysis with the Arrow-Trerotola Percutaneous Thrombolytic Device. J Vasc Interv Radiol 2001;12(10):1157-65.
17. Inston N, Al Shakarchi J, Khawaja A, Jones R. Maintaining Patency of Vascular Access for Haemodialysis. Cardiovasc Eng Technol 2017; 8(3):240-3.

18. Koraen-Smith L, Krasun M, Bottai M, Hedin U, Wahlgren CM, Gillgren P. Haemodialysis access thrombosis: Outcomes after surgical thrombectomy versus catheter-directed thrombolytic infusion. J Vasc Access. 2018;19(6):535-41.
19. Tseke P, Kalyveza E, Politis E, Giapraka N, Andriopoulos C, Balitsari A et.al. Thrombolysis with alteplase: a non-invasive treatment for occluded arteriovenous fistulas and grafts. Artif Organs. 2011 Jan;35(1):58-62.
20. Aydin E, Bademci MS, Kocaaslan C. Comparison of pharmacomechanical and surgical interventions for thrombosed native arteriovenous fistulas. Turk Gogus Kalp Damar Cerrahisi Derg 2020; 28(4):609-14.
21. Koraen-Smith L, Krasun M, Bottai M, Hedin U, Wahlgren CM, Gillgren P. Haemodialysis access thrombosis: Outcomes after surgical thrombectomy versus catheter-directed thrombolytic infusion. J Vasc Access. 2018;19(6):535-541.
22. Hilleman D, Campbell J. Efficacy, safety, and cost of thrombolytic agents for the management of dysfunctional hemodialysis catheters: a systematic review. Pharmacotherapy 2011; 31(10):1031-40.
23. Wan Z, Xiang R, Wang H, Zhong Q, Tu B. Comparative efficacy and safety of local and peripheral venous thrombolytic therapy with urokinase for thrombosed hemodialysis arteriovenous fistulas. Exp Ther Med 2019;17(5):4279-84.
24. Xie H, Kim K, Aglyamov SR, Emelianov SE, Xunchang C, O'Donnell M et al. Staging deep venous thrombosis using ultrasound elasticity imaging: animal model. Ultrasound Med Biol 2004;30:1385-96.
25. Fineschi V, Turillazzi E, Neri M, Pomara C, Riezzo I. Histological age determination of venous thrombosis: a neglected forensic task in fatal pulmonary thrombo-embolism. Forensic Sci Int. 2009;186(1-3):22-8.
26. Stanford SN, Sabra A, D'Silva L, Lawrence M, Morris RHK, Storton S. The changes in clot microstructure in patients with ischaemic stroke and the effects of therapeutic intervention: a prospective observational study. BMC Neurol 2015;15:35.
27. Oklu R, Wicky S. Catheter-directed thrombolysis of deep venous thrombosis. Semin Thromb Hemost 2013;39:446-51.
28. Goktay AY, Senturk C. Endovascular Treatment of Thrombosis and Embolism. Adv Exp Med Biol 2017;906:195-213.
29. Andriani M, Drago G, Bernardi AM, Da Porto A, De Luca M, Riegler P et al. Recombinant tissue plasminogen activator (rt-PA) as first-line therapy for declotting of haemodialysis access. Nephrol Dial Transplant. 1995;10(9):1714-9.
30. Regus S, Lang W, Heinz M, Uder M, Schmid A. Benefits of Long Versus Short Thrombolysis Times for Acutely Thrombosed Hemodialysis Native Fistulas. Vasc Endovascular Surg 2017; 51(5): 233-9.
31. Chang R, Horne MK, 3rd, Shawker TH et al. Low-dose, once-daily, intraclot injections of alteplase for treatment of acute deep venous thrombosis. J Vasc Interv Radiol 2011;22(8): 1107-16.