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Thrombolysis With Alteplase: A Non-Invasive Treatment for Occluded Arteriovenous Fistulas and Grafts

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Abstract: Thrombolysis with recombinant tissue type plasminogen activator (t-PA) has been successfully used in occluded arteriovenous (AV) hemodialysis grafts and tunneled catheters, especially as an adjunctive regimen to invasive or semi-invasive procedures. We performed a retrospective study to evaluate the effectiveness and outcomes of thrombolysis with t-PA in occluded AV hemodialysis accesses. We used low doses of t-PA in 40 cases of thrombosed AV fistulas and grafts. Primary success was noted in 55% of the cases ensuring patency rates of 30 and 90 days at 90.9 and 69.8%, respectively. Inflammation (increased C-reactive protein concentration) and shorter functioning time of AV access were independently associated with primary outcome, whereas there was no difference in outcome between AV fistulas or grafts. No major complications were noted. We conclude that the use of t-PA is a safe and easy treatment for clotted AV accesses that can be applied in an outpatient setting.
Key Words: Hemodialysis—Alteplase—Vascular access—Occlusion.

Functioning vascular access is crucial for hemodialysis (HD) patients' morbidity and mortality. Approximately 16–23% of HD patients' hospitalizations are related to vascular access complications (1). The most common complication is thrombosis, which accounts for 80–85% of vascular access loss (1,2).

Recent data from the United States Renal Data System (USRDS) report in 2009 suggest that the morbidity and the annual cost of hospitalization are much higher in patients with central venous catheters (CVCs) and grafts than in patients with arteriovenous (AV) fistulas. The access event costs per person per year for patients with CVC and AV grafts were estimated at US $5960 and $7451, respectively, whereas the corresponding costs for patients with AV fistulas were estimated at $3194 (3).

Thrombolysis with alteplase (recombinant tissue-type plasminogen activator [t-PA]) has been successfully used in clotted CVC and AV grafts in various regimens and techniques, such as pulse-spray thrombolysis or lyse-and-wait or as a complementary treatment to invasive procedures, that is, angioplasty (4–6). However, there are limited data regarding the use of t-PA in the treatment of occluded AV fistulas (7,8).

We retrospectively analyzed the results of a thrombolysis protocol with t-PA (Actilyse, Boehringer Ingelheim, Ingelheim am Rhein, Germany), which was applied for the last 3 years in clotted AV fistulas and grafts in our department.

PATIENTS AND METHODS

Forty patients, 25 (62.5%) males and 15 (37.5%) females with median age of 71 years (range 25–84), were recruited to our study. All patients were on chronic HD for a median time of 20 months (range 3–120). All patients consented to the study and the local ethics committee approved the study protocol.

Thrombosis diagnosis was based on clinical criteria (absence of thrill or bruit) and was confirmed by ultrasound. Thrombolysis was performed in all cases under a standard protocol in the dialysis unit, as described below, as soon as diagnosis was made and no later than 72 h. We postponed thrombolysis for about 1 h in cases of previous repeated punctures in

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efforts for cannulation by the staff, due to the risk for hemorrhage. Shortly after the thrombotic event, especially in patients with clinical signs of stenosis, we performed further workup, which included angiography with placement of stents, or surgical interventions (i.e., thrombectomy, surgical repair of AV access, etc.), when indicated.

Outcomes regarding thrombolysis success and patency time were recorded in all cases for a maximum of 3 years. Predictors of immediate outcome of thrombolysis procedure (success or no) were identified using logistic regression analysis. Stepwise analysis was used to identify independent predictors of thrombolysis success. During follow-up, patients were censored at death with functioning AV access, when a surgical procedure to generate a new AV access was performed, while no reclotting was present, or when percutaneous transluminal angioplasty (PTA) with stent placement was performed. Reclotting of AV access was defined as an event. Kaplan–Meier analysis was applied to estimate median patency time of AV access after successful thrombolysis and probability of reclotting. Statistical analysis was carried out using STATA version 9.1 (StataCorp, College Station, TX, USA).

Thrombolysis protocol

Fifty milligrams of t-PA were dissolved with normal saline 0.9% to prepare 100 mL of solution (0.5 mg/mL), which was divided into 25 syringes of 4 mL and kept frozen in –18°C; in that way, they were ready to use when needed. A tourniquet was placed to prevent leak of the thrombolytic agent to systemic circulation and to prolong its contact with the clot. The vascular access was entered using a 21G butterfly needle. t-PA was infused as proximal as possible to the clot retrograde in relation to anastomosis, as shown in Fig. 1, in case of AV fistulas, whereas in AV grafts, two needles were placed in a retrograde manner, as shown in Fig. 2. Manual manipulation was performed in order to soften the clot during t-PA infusion. The procedure could be repeated if necessary with a second prepared syringe until the maximum dose of 6 mg of t-PA. After successful thrombolysis, the patient could be dialyzed immediately, if necessary, and low molecular weight heparin (Tinzaparin Sodium, Innohep, Leo Pharmaceutical Products Hellas Ltd., Athens, Greece) in a dose of 50 IU/Kg (body weight) was prescribed for 7 consecutive days.

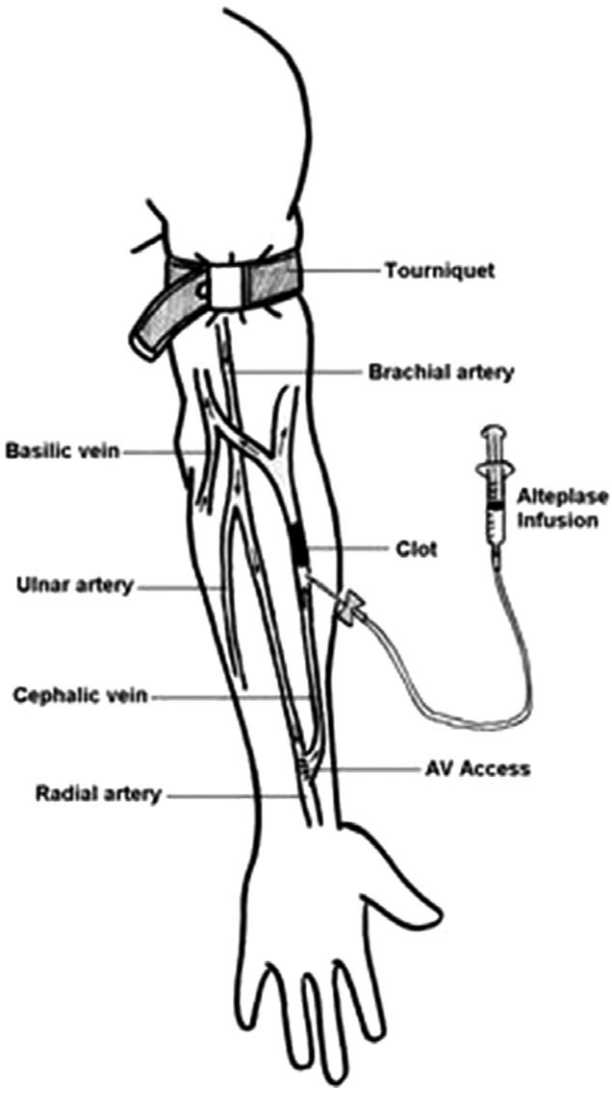

FIG. 1. Thrombolysis with tissue-type plasminogen activator in occluded autologous arteriovenous (AV) fistula. Butterfly needle is inserted as proximal as possible to the clot retrograde in relation to anastomosis. A tourniquet is placed in the arm to prevent leak of the thrombolytic agent to the systemic circulation and to prolong its contact with the clot.

RESULTS

Forty cases of thrombosis were recorded, 27 (67.5%) of them involved AV grafts and 13 (32.5%) autologous AV fistulas. The average dose of t-PA used was 3.02 ± 1.54 mg. Thrombolysis, resulting in immediate patency, was achieved in 22 of 40 cases (55%), 8 in 13 AV fistulas (61.5%), and 14 in 27 (51.8%) in AV grafts. Clinical and biochemical characteristics of the patients are presented in Table 1. Statistically significant predictors of thrombolysis success in univariate logistic regression analysis are presented in Table 2. Sex, previous treatment with antiplatelets, hemoglobin, and blood urea nitrogen (BUN) concentrations were significantly associated with thrombolysis outcome ($P < 0.05$). C-reactive protein (CRP) was

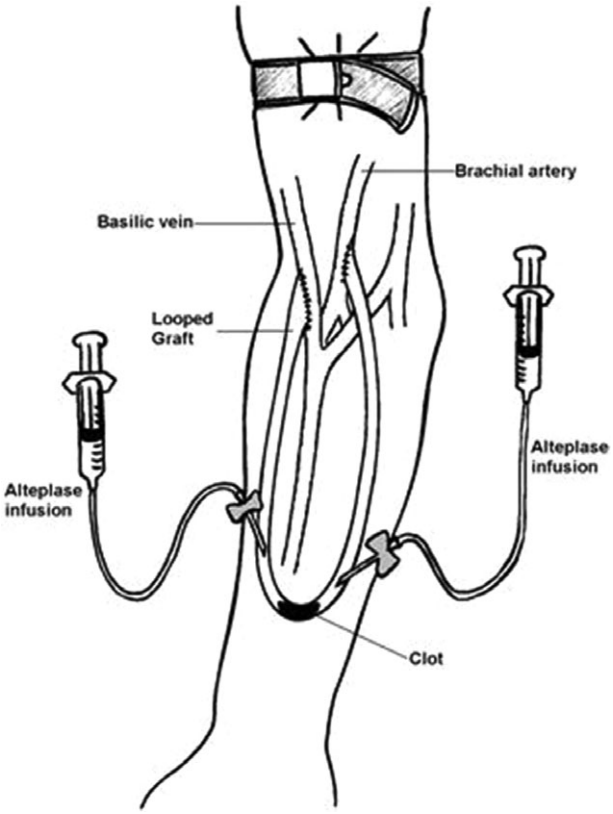

FIG. 2. Thrombolysis with tissue-type plasminogen activator in an occluded arteriovenous graft. Two butterfly needles are inserted on the edges of the graft, as proximal as possible to the clot.

marginally correlated with outcome in univariate analysis ($P = 0.068$). In order to identify independent predictors of thrombolysis success, we performed stepwise multivariate logistic regression analysis adjusted for variables with $P < 0.1$ (Table 3).

Increase in CRP (odds ratio: 1.25 per unit increase in log scale, $P = 0.014$) and decrease in time since AV access generation (odds ratio: 0.11 per month increase in time in log scale, $P = 0.016$) were identified as independent risk factors for a nonsuccessful procedure.

In 7 of 18 patients with nonsuccessful thrombolysis, PTA with stent placement was performed, and in the rest, 11 patients, a new AV access was generated.

Thrombolysis procedure was not complicated with any side effects in 18 of 40 cases (45%), whereas 17 patients (42.5%) complained of local pain, and local hematoma was present in five of total cases (12.5%). No hemorrhage or systemic reactions were noted in any of the cases.

In 10 of 22 patients (45.5%), there was no reclotting during follow-up. Reclotting was noted in 12 of 22 patients (55.5%) in a median time of 6 months after successful thrombolysis as shown in Fig. 3. Patency rates at 30 and 90 days were 90.9 and 69.8%, respectively. Due to the small number of events, we were unable to proceed in further statistical analysis for the identification of risk factors for reclotting.

DISCUSSION

Salvage of an occluded vascular access is of utmost importance for chronic HD patients. The studies by Ahmed et al. (9) and Andriani et al. (10) were two of the first reports of the use of t-PA in the thrombolysis of occluded AV accesses using maximum doses of 30 mg (9) and average doses of 21 mg (10). Since then, most of the studies published in the literature involved invasive or semi-invasive (pharmacomechanical) protocols of thrombolysis using t-PA as adjunctive treatment (6,8). Studies regarding thrombolysis procedures or outcomes are limited in the

TABLE 1. *Patient characteristics*

Sex	15 females (37.5%) 25 males (62.5%)
Age	Median 71 (range 25–84)
Cumulative time on HD	Median 20 (range 3–120)
Patency time since thromboses	Median 20 (range 3–120)
Type of AV access	13 AVFs (32.5%) 27 AVGs (67.5%)
Location of AV access	20 (50%) forearm 18 (45%) upper arm 2 (5%) lower extremities
Comorbidities	
Diabetes mellitus	17 (42.5%)
Hypertension	30 (75%)
Coronary heart disease	19 (47.5%)
History of:	
CVC*	25 (62.5%)
Previous AV access	18 (45%)
(in same extremity)	11 (27.5%)
Clinical signs of stenosis†	14 (35%)
Treatment with antiplatelets	22 (55%)
Laboratory findings	
Hemoglobin (g/dL)	11.7 ± 0.91
BUN (mg/dL)	66.3 ± 16.6
Creatinine (mg/dL)	7.85 ± 2.22
i-PTH (pg/mL)	Median 210 (range 48–903)
Calcium (mg/mL)	8.94 ± 0.59
Phosphorus (mg/mL)	5.62 ± 1.29
Calcium × Phosphorus product	Median 50 (range 25–92)
CRP (mg/mL)	Median 2.15 (range 0.48–7.97)

Normally distributed continuous variables are described by mean ± SD, whereas skewed variables are described by median and range.

* History of central venous catheters placement.

† Clinical signs of preexisting stenosis were considered the following: progressive reduction in blood flow, increase in venous pressure or significant decrease in venous pressure implying high recirculation rate, prolonged bleeding after needle withdrawal, altered features of bruit or thrill.

AV, arteriovenous; AVF, AV fistula; AVG, AV graft; BUN, blood urea nitrogen; CRP, C-reactive protein; CVC, central venous catheter; HD, hemodialysis; i-PTH, intact parathyroid hormone.

TABLE 2. *Unadjusted univariate logistic regression analysis for failure versus success*

Variable	Odds ratio	*P* value
Sex (male vs. female)	0.23	0.038
Age (per year)	0.99	0.876
Cumulative time in HD	0.91	0.804
Patency time since thromboses	0.74	0.338
AV-graft vs. fistula	1.48	0.565
Location of AV access (1 vs. 0)*	0.64	0.493
Comorbidities (yes/no)		
Diabetes mellitus	1.15	0.822
Hypertension	1.31	0.714
Coronary heart disease	0.80	0.726
History of		
CVC (yes/no)	1.63	0.521
Previous AV access (yes/no)	1.44	0.566
Clinical signs of stenosis	1.01	0.641
Treatment with antiplatelet agents	0.29	0.068
Laboratory findings		
Hemoglobin(g/dL)	1.01	0.028
BUN (mg/dL)	1.03	0.047
Creatinine (mg/dL)	0.81	0.231
i-PTH (pg/mL)	0.99	0.514
Calcium (mg/mL)	0.69	0.537
Phosphorus (mg/mL)	1.25	0.403
Calcium × phosphorus product	1.01	0.477
CRP (mg/mL)	1.09	0.068

All variables coded yes/no were analyzed as binary variables with 1 standing for yes and 0 standing for no (reference value).

* Locations of AV access were coded as follows: 0 = forearm, 1 = upper arm. Analysis did not include lower extremities due to small number (two cases).

literature, involving small number of patients, and they are not prospective or randomized. Under this perspective, we believe that our study, despite its small number of participants, adds significant information in this era.

We describe a simple, noninvasive method for the treatment of thrombosed AV fistulas and grafts, which can be performed by noninterventionists in an outpatient setting. Thrombolysis with t-PA seems to be safe for HD patients, as we noted that in the vast majority of our cases, thrombolysis was either uneventful or complicated with local pain. Only 5 of 40 patients developed local hematoma, without requiring hospitalization or special treatment. In the study by Andriani et al. (10), local bleeding occurred in 16% of the patients, whereas in the study by Ahmed et al. (9), serious bleeding requiring compression in AV access, which resulted in reclotting, was

TABLE 3. *Adjusted multivariate logistic regression analysis for failure versus success*

Variable	Odds ratio	*P* value
CRP (mg/mL-log scale)	1.25	0.014
Patency time since thromboses (in months-log scale)	0.11	0.011

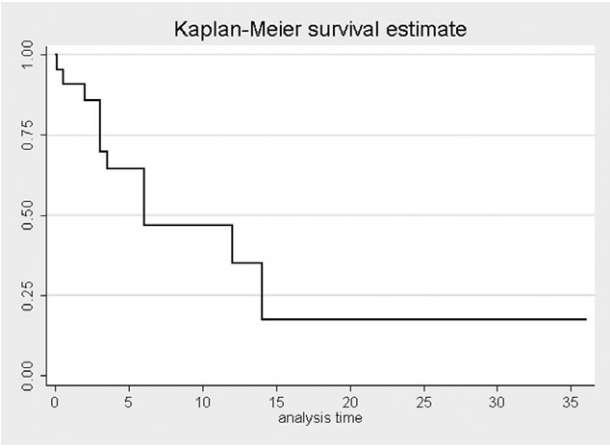

FIG. 3. Kaplan–Meier survival analysis graph showing primary patency time after successful thrombolysis (*x*-axis) and estimated survival (= no reclotting) probability.

reported in 1 in 15 patients. Furthermore, in semi-invasive protocols involving combination of pharmacological thrombolysis with balloon angioplasty (7,8), more serious complications, which involved pulmonary edema (1 in 25), arterial embolism (1 in 25), and rupture of vessel (1 in 16), have been reported.

Our findings show evidence of the beneficial use of low doses of t-PA (even lower than previously reported [7,10]) for the thrombolysis of clotted AV fistulas and grafts, eliminating the need for invasive treatments, or ensuring time for interventions, without need for CVCs placement. Previous studies on clotted AV grafts (11) have reported 72 and 57% primary patency rates in 30 and 90 days, respectively, using higher doses of t-PA. Schon et al. (8) reduced the dose of t-PA to an average of 2.3 mg per procedure and reported a high primary success rate of 92 and 94% in their previous report (7). However, the main reason for the high primary success rate in these studies is that thrombolysis in all cases was followed by PTA with high-pressure balloons.

CONCLUSIONS

In this series, we noted that the outcome of thrombolysis procedure was independently and inversely related to the time since AV access generation. Earlier AV access failure could be possibly related to poor access maturation, which, in turn, is associated with the vessels' quality and the existence of certain risk factors (i.e., age, female gender, diabetes, etc.) (12), or even the surgeon's experience (13).

To our knowledge, this is the first study to report evidence of association between CRP and thrombolysis outcome. It is possible that inflammation is

implicated in the functional and structural changes in the vascular bed that predispose to arterial stiffness, vascular calcification, and stenosis. Calcified and stiffened arteries may not remodel appropriately to ensure AV access function and longevity (14). Furthermore, the inflammatory process and excessive mechanical stress close to the AV anastomosis contributes to vascular smooth cell proliferation and neointimal hyperplasia that has been recently associated with early AV access failure (15) or restenosis after PTA (16). Experimental data suggest beneficial effects of locally administered antiproliferative agents and antioxidants to the inhibition of neointimal hyperplasia (17).

Anticipating results in human studies, our results suggest that thrombolysis with t-PA is a safe, easy, and noninvasive choice of treatment for occluded AV fistulas and grafts.

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