Low-dose Alteplase in the treatment of malfunctioning cuffed tunneled catheters for hemodialysis patients

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Objective
To study the efficacy of using low-dose thrombolytic agent Alteplase on restoring patency of thrombotic or occluded cuffed tunneled catheters (CTCs) without the need for more invasive procedures.
Patients and methods
We performed a prospective study of 35 patients with malfunctioning CTCs during the period from August 2018 to August 2021, who were attending the emergency room or outpatient clinic at Ain Shams University Hospitals. We excluded patients having absolute or relative contraindication to thrombolytic therapy, infected CTCs, and CTCs with malposition. Clinical records included patient demographics, etiology, and any previous catheter insertion. Procedural details included access site, equipment used, procedural outcomes, and complications. After providing written informed consent, initially we used 2.5 mg of Alteplase in each limb of CTCs. Each limb was connected to an infusion pump at a rate of 0.5 mg Alteplase per hour. CTCs were tested at 6, 12, 18, and 24 h; smooth injection and withdrawal of each limb were the primary end points. Successful hemodialysis session was the secondary end point. Follow-up of patients up to 3 years was recorded.
Results
All our patients were permanently dependent on CTCs. There were 19 males and 16 females, with ages ranging between 18 and 65 years (mean±SD, 55.91 ± 8.20 years). We had 21 femoral, three right internal jugular, and 11 left internal jugular CTCs. Patients were treated with a low dose of thrombolytic agent Alteplase with a mean±SD 9.83 ± 5.03 h and had a median follow-up of 36 months. The median duration of CTCs after the procedure was 24 months. Only three (8.5%) CTCs were changed.
Conclusions
Treating malfunctioning CTCs with low-dose Alteplase is an excellent choice. The technique has good 1, 2, and 3 years of follow-up and is associated with significant clinical improvement and few complications.

Keywords:
Alteplase, cuffed tunneled catheters, hemodialysis, malfunctioning, thrombolytic

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Introduction

Hemodialysis is the most common treatment for patients with chronic kidney disease [1]. Lifespan of patients is specifically related to the quality of dialysis. It depends on the reliability and integrity of vascular access for the patient. This pivotal connection is known as the hemodialysis vascular access. The perfect hemodialysis access is the one that provides reliable, complication free access to deliver endorsed dialysis [2].

There are different modalities of vascular access in clinical practice, such as tunneled/nontunneled central venous catheters, cuffed/noncuffed central venous catheters, native arteriovenous fistulae, and arteriovenous grafts. The choice of vascular access is decided by several clinical factors, which include the patient's vascular status, comorbidity, nutritional status, functional performance, physician's inclination, and timing of referral by a nephrologist [3]. Cuffed tunneled catheters (CTCs) often act as a bridge to permanent access for hemodialysis. In 2006, the National Kidney Foundation Kidney Disease Outcomes Quality Initiative (KDOQI) advised against long-term TDC utilize without a plan for permanent access creation. In 2019, the recommendations were updated to be more patient focused [4].

KDOQI considers using tunneled CTCs for long-term or uncertain durations as follows:

(1) Several prior failed arteriovenous accesses with no accessible alternatives.
(2) Valid patient preference whereby use of an arteriovenous access would limit the quality of life.
(3) Limited life expectancy as in old age or end-stage cancer patients.
(4) Absence of arteriovenous access creation options due to either inflow artery and/or outflow vein problems (e.g. severe arterial occlusive disease, noncorrectable central venous outflow occlusion) or in infants/children.
(5) Special medical circumstances [2].

Tragically, hemodialysis catheters have a brief functional life span. At the end of a 1-year follow up, at least 50% of catheters failed to perform as required to attain satisfactory hemodialysis sessions. This rate of failure highlights the significance of suitable care of hemodialysis catheters. Management of catheter-related complications is a critical challenge that must be managed within in order to maintain convenient and efficient hemodialysis [5]. The major complications of catheters include thrombosis and infection. Around 50% of hemodialysis catheters fail within 1 year. Two-thirds of the failures are due to thrombosis [6].

Therefore, CTCs dysfunction (previously defined by 2006 KDOQI guideline13 as 'failure to achieve and keep an extracorporeal blood flow of ≥300 ml/min at a pre-pump arterial pressure more negative than −250 mm Hg) endures. Besides increases in arterial and venous pressures enrolled by the dialyzer that requires a decrease in blood flow, CTC dysfunction can result in significant recirculation, leading to poor clearance. Left untreated, such CVCs require premature removal when they are nonfunctional [7]. Over a period of from days even to months, collagen is deposited near the tip from the venous vessel wall where the CTC is located. If clotting surpasses the capacity of endogenous fibrinolytic system, consequent CTC thrombosis will result [8].

Upkeep of CTC patency is fundamental to provide adequate hemodialysis in patients requiring CTCs on either a temporary or long-term basis. A common complication of the CTC is dysfunction, which is associated with decreased dialysis adequacy and increased risk of catheter-related blood stream infections. Interventions to prevent and treat CTC dysfunction can be classified as medical and mechanical interventions. Medical interventions are further subdivided into conservative maneuvers and pharmacologic interventions, for example (Alteplase) actilyse, which is a recombinant human tissue plasminogen activator (rt-PA) [2].

Alteplase (tPA) is an effective well-tolerated thrombolytic agent used in the lysis of acute thromboembolism. FDA-approved indications for Alteplase incorporate pulmonary embolism, ST-segment elevation myocardial infarction, and ischemic stroke within 3 h of appearance of symptoms and reestablishment of patency in dysfunctional CTCs [9]. As a regrade dosage of rt-PA in pulmonary embolism, The 2019 Collaborative (European Society of Cardiology and European Respiratory Society) Clinical Practice Guideline on the Diagnosis and Management of Acute Pulmonary Embolism mentions an loading infusion regimen of rt-PA of 0.6 mg/kg (maximum, 50 mg) [10].

Here, we try to focus on using a small dose of rt-PA in the treatment of CTC dysfunction, especially for those patients depending on them for long time either due to exhausted options for the creation of arteriovenous shunting or due to medical problems (e.g. heart failure). Besides, the follow-up of those catheters was recorded to add to literature efficacy of such technique.

Patients and methods

This study was accepted by the Ethics Committee of Ain Shams University Hospital .We performed a prospective study of 35 malfunctioning/nonfunctioning CTCs of 35 patients. The study period was from August 2019 to August 2021 on patients attending the emergency room or the outpatient clinic at Ain Shams University Hospitals.

Inclusion criteria

(1) Malfunctioning or occluded CTCs.
(2) CTC-dependent patients.

Exclusion criteria

(1) Absolute contraindications including: prior intracranial hemorrhage, known cerebral arteriovenous malformation, known cerebral neoplasm (primary or metastatic), ischemic stroke within 3 months, suspected aortic dissection, active bleeding or bleeding diarrhea (excludes menses), and significant trauma within the past 3 months.
(2) Relative contraindications including: severe uncontrolled hypertension on presentation (systolic blood pressure >180 mmHg or diastolic blood pressure >110 mmHg), prolonged CPR more than 10 min, history of prior ischemic stroke more than 3 months, major surgery less than 3 weeks, recent intracranial hemorrhage (within 2–4 weeks), noncompressible vascular punctures,

pregnancy, active peptic ulcer, and current use of anticoagulants.
(3) Infected CTCs.
(4) CTC malposition.

Clinical records included patient demographics, etiology, and any previous catheter insertion. Procedural details included access site, equipment used, procedural outcomes, and complications.

After providing written informed consent, initially we used actilyse (Alteplase), which is a rT-PA, 2.5 mg in each limb of CTCs. Then each limb was connected to an infusion pump at a rate of 0.5 mg rT-PA per hour.

CTCs were followed up and tested in intermediate ICU at 6, 12, 18, and 24 h; smooth injection and withdrawal of each limb were the primary end points. Successful hemodialysis session (mean blood flow, ≥300 ml/min during each treatment) was the secondary end point. Follow-up of patients up to 3 years was recorded.

Patients were followed up at a vascular surgery clinic for 1, 2, and 3 months on a small dose of oral anticoagulant.

Definitions used:

Malfunctioning/nonfunctioning CTCs: a catheter that failed to have 4 h consecutive successful hemodialysis session.

Infected CTCs: a catheter with local signs of infection, or systemic signs of infection claimed to the catheter.

Minor bleeding: bleeding that does not require intervention or blood transfusion.

Results

We collected data of 35 patients (35 malfunctioning CTCs) who underwent low-dose thrombolytic therapy using Alteplase. Demographic data (Table 1) showed that 19 (54.3%) patients were males. Hypertension was the dominant comorbidity (27, 77.1%). All of them was dependent on the CTCs, 25 (71.4%) patients due to exhausted sites for arteriovenous shunting, 10 (28.5%) patients unsuitable cardiac conditions to tolerate hyperdynamic circulation caused by arteriovenous stunting, and one (2.8%) patient was refused arteriovenous shunting though he was fit for it.

Thrombosis of the catheter was significantly affected by the site of the catheter as the least site of thrombosis was in the right internal jugular vein (IJV)

Table 1 Demographic data of the patients

	N=35
Age (years)	
Median (IQR)	57 (53–61)
Range	18–65
Sex [*n* (%)]	
Female	16 (45.7)
Male	19 (54.3)
Smoking [*n* (%)]	
No	20 (57.1)
Yes	15 (42.9)
DM [*n* (%)]	
No	9 (25.7)
Yes	26 (74.3)
HTN [*n* (%)]	
No	8 (22.9)
Yes	27 (77.1)
Polycyctic kidney disease [*n* (%)]	
No	31 (88.6)
Yes	4 (11.4)
ISHD [*n* (%)]	
No	16 (45.7)
Yes	19 (54.3)

DM, diabetes mellitus; HTN, hypertension; IQR, interquartile range.

Table 2 Cuffed tunneled catheter related data

	N=35 [*n* (%)]
Site of CTCs	
Femoral	21 (60.0)
Left jugular	11 (31.4)
Right jugular	3 (8.6)
Duration of CTCs (months)	
Median (IQR)	24 (12–36)
Range	1–42
Average of procedure (h)	
Median (IQR)	8 (6–12)
Range	6–12
Adverse events	
No adverse events	32 (91.4)
Minor bleeding	3 (8.6)
Change CTC	
No CTC changes	32 (91.4)
CTC changes	3 (8.6)

CTC, cuffed tunneled catheter; IQR, interquartile range.

three (6.8%) and the highest affected site was in the femoral vein 21 (60%) (Table 2). CTC incidence of thrombosis is significantly affected by the duration of catheter insertion (mean±SD, 23.49 ± 10.88 months) (Table 2). The short time of continuous thrombolysis was recorded (mean±SD, 9.83 ± 5.03 h) (Table 2) with minimal incidence of minor bleeding, three (8.6%) at the exit site of CTCs (Table 2). Only three CTCs failed to resume function after 24 h of continuous infusion of Alteplase (Table 2). The results showed an insignificant relation between age, sex, smoking, and adverse effects of thrombolysis (Table 3). Comorbidities such as hypertension, diabetes, polycystic kidney, and ischemic

Table 3 Relation of patient's data to adverse events

	Adverse events [*n* (%)]		Test value	*P* value	Significance
	No adverse events	Minor bleeding			
	N=32	*N*=3			
Age (years)					
Median (IQR)	57 (53.5–60.5)	54 (18–65)	–0.472≠	0.637	NS
Range	48–65	18–65			
Sex					
Female	15 (46.9)	1 (33.3)	0.203*	0.653	NS
Male	17 (53.1)	2 (66.7)			
Smoking					
No	17 (53.1)	3 (100.0)	2.461*	0.117	NS
Yes	15 (46.9)	0			
DM					
No	8 (25.0)	1 (33.3)	0.100*	0.752	NS
Yes	24 (75.0)	2 (66.7)			
HTN					
No	8 (25.0)	0	0.972*	0.324	NS
Yes	24 (75.0)	3 (100.0)			
Polycystic kidney disease					
No	29 (90.6)	2 (66.7)	1.555*	0.212	NS
Yes	3 (9.4)	1 (33.3)			
ISHD					
No	14 (43.8)	2 (66.7)	0.580*	0.446	NS
Yes	18 (56.2)	1 (33.3)			

DM, diabetes mellitus; HTN, hypertension; IQR, interquartile range. *χ^2 tests. ≠Mann–Whitney test. *P* value more than 0.05: nonsignificant (NS); *P* value less than 0.05: significant (S); *P* value less than 0.01: highly significant (HS).

Table 4 Relation of cuffed tunneled catheter data to adverse events

	Adverse events [*n* (%)]		Test value	*P* value	Significance
	No adverse events	Minor bleeding			
	N=32	*N*=3			
Site of CTCs					
Femoral	19 (59.4)	2 (66.7)			
Right jugular	2 (6.2)	1 (33.3)	3.403*	0.182	NS
Left jugular	11 (34.4)	0			
Duration of CTCs (months)					
Mean±SD	24 (15–36)	24 (12–30)	–0.240≠	0.810	NS
Range	1–42	12–30			
Average of procedure (h)					
Mean±SD	8 (6–12)	6 (6–8)	–1.192≠	0.233	NS
Range	6–12	6–8			
Change CTCs					
No CTCs changes	30 (93.8)	2 (66.7)	2.567*	0.109	NS
CTCs changes	2 (6.2)	1 (33.3)			

CTC, cuffed tunneled catheter. *χ^2 tests. ≠Mann–Whitney test. *P* value more than 0.05: nonsignificant (NS); *P* value less than 0.05: significant (S); *P* value less than 0.01: highly significant (HS).

heart disease (ISHD) have an insignificant effect on the adverse effects of thrombolysis (Table 3). The results showed insignificant relation between the sites, duration of the catheter, duration of the procedure, the need to change the catheter, and the adverse effects of thrombolysis (Table 4). Also, our results showed an insignificant relationship between demographic data and change of CTCs. Median follow-up of 36 months and median duration of CTCs after the procedure was 24 months (Table 5).

Discussion

CTCs are important means of hemodialysis and are associated with both infectious and noninfectious complications, leading to increased morbidity and mortality in hemodialysis patients. Infection is a major chronic complication which may include the entry site, blood stream, and tunnel infections. Noninfectious complications include the pneumothorax and the hemithorax, which may occur at the time of insertion,

Table 5 Relation of changing cuffed tunneled catheter to catheter data

	Change CTCs [*n* (%)]		Test value	*P* value	Significance
	No CTC changes	CTC changes			
	N=32	*N*=3			
Site of CTCs					
Femoral	19 (59.4)	2 (66.7)			
Right jugular	3 (9.4)	0	0.309*	0.857	NS
Left jugular	10 (31.2)	1 (33.3)			
Duration of CTCs (months)					
Median (IQR)	24 (18–33)	12 (12–36)	–0.510≠	0.610	NS
Range	1–42	12–36			
Average of procedure (h)					
Median (IQR)	8 (6–12)	6 (6–8)	–1.192≠	0.233	NS
Range	6–12	6–8			
Adverse events					
No adverse events	30 (93.8)	2 (66.7)	2.567*	0.109	NS
Minor bleeding	2 (6.2)	1 (33.3)			

CTC, cuffed tunneled catheter. *χ^2 tests. •Independent *t* test. ≠Mann–Whitney test. *P* value more than 0.05: nonsignificant (NS); *P* value less than 0.05: significant (S); *P* value less than 0.01: highly significant (HS).

dysfunction due to mechanical issues, or material fatigue that may develop over the duration of catheter use. Another definition of CTC dysfunction is thrombotic occlusion due to nonheparinization resulting in poor blood flow, inadequate dialysis, and other serious complications [1].

Prompt removal of infected CTCs is extremely necessary in the event that conservative measures to save the catheter were failed [4]. However, it is not the same for malfunctioning CTCs, changing malfunctioning over a guide wire is attempted by many surgeons; this approach may result in subsequent problems like infection or failure to pass the catheter over the wire due to stenosis. Limited number of alternative access to patent deep veins should be in mind, so dealing with previously functioning CTCs – especially if it is inserted for months and free of infection – is more safe and considerable than changing it. Vats reported that intraluminal thrombosis was the primary reason for CTC dysfunction, with 17–33% requiring untimely removal of the catheter, 30–32 contributing to access loss in 30–40% of patients [11].

There is no doubt that patients on regular hemodialysis are fragile with certain angipathy; therefore, low-dose thrombolytic agents can be used safely to successfully restore patency in thrombotic or occluded catheters without the need for a more invasive procedure. We focused on using low-dose rT-PA in saving thrombosed CTCs or distal vein thrombosis without exposure to imaging and risk of radiation followed by a low-dose oral anticoagulant. Vats also reported treatment of thombosed CTCs using rt-PA with a success rate of 66%. In our study changing of CTCS was only in three (8.5%) patients; this failure may be due to occlusion of the vein proximal to the tip of the catheter or blockage of the catheter lumen with nondissolvable material as the three CTCs was placed in a new site because the guide wire failed to pass through the catheter lumen.

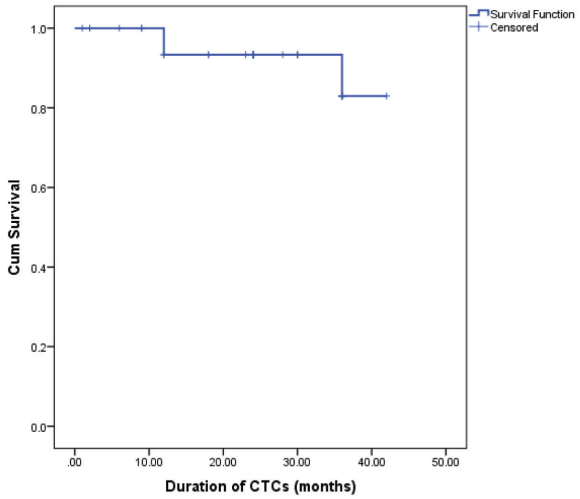
So, we minimized the risk of CTC change; also, it is easy to redo it with a low cost than changing it in some centers. The ultimate goal is maintaining the patency of same CTC, as its site may be occluded after removal of the catheter due to fibro-epithelial tracks or subclinical inflammation due to prolonged contact of the catheter with the epithelial venous layer [6]. In our center, we attempt to place the CTCs in the internal jugulars as the first choice; however, most of malfunctioning CTCs were inserted in the femoral veins, this reflects that we have to adopt an effective protocol concerning catheter thrombosis prophylaxis for femoral vein inserted catheters.Also arteriovenous shunting should be created and matured before the onset of hemodialysis. All efforts should be used to maintain every single arteriovenous shunt not to exhaust the other sites, especially for young patients [2].

For patients expected to use CTCs permanently all efforts should be concerned to avoid infection, and for malfunctioning CTCs free of infection with good position and previously functioning well we have to try solving this problem before changing it.

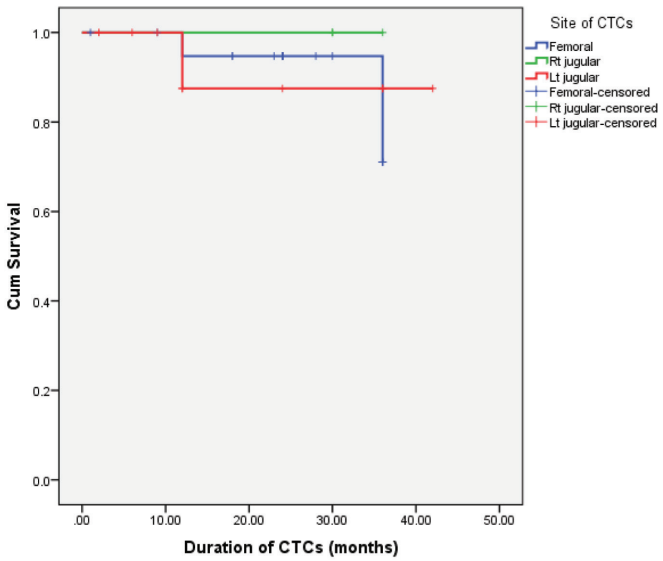
Adding a low dose of anticoagulant after thrombolysis was enough to keep the CTC function for several months (Fig. 1).

Figure 1

	Total N	N of Events	Mean	SE	95% CI		Change CTCS at		
					Lower	Upper	1 year	2 years	3 years
Total patients	35	3	39.378	1.459	36.518	42.237	94.70%	94.70%	71.10%



Site of CTCs	Total N	N of Events	Mean	SE	95% CI		Change CTCS at			Log Rank test		
					Lowe r	Uppe r	1 year	2 years	3 years	X^2	P-value	Sig.
Femoral	21	2	34.737	1.739	31.329	38.145	94.7%	94.7%	71.1%	0.370	0.831	NS
Rt jugular	3	0	-	-	-	-	100.0 %	100.0 %	100.0 %			
Lt jugular	11	1	38.250	3.508	31.375	45.125	87.5%	87.5%	87.5%			



Kaplan–Meier analysis for the relation between the site of CTCs and change of CTCs with the duration of CTCs. CTC, cuffed tunneled catheter.

Conclusion

Using low-dose Alteplase is extremely safe and effective in treating malfunctioning or occluded CTCs for hemodialysis patients. It is a noninvasive short-time procedure with rapid recovery. It gives satisfactory follow-up for a long time. Saving every single access to deep veins is life saving for hemodialysis-dependent patients.

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Conflicts of interest
There are no conflicts of interest.

References

1 Poinen K, Quinn RR, Clarke A, Ravani P, Hiremath S, Miller LM, Blake PG, Oliver MJ. Complications from tunneled hemodialysis catheters: a Canadian observational cohort study. Am J Kidney Dis 2019; 73: 467–475.

2 Lok CE, Huber TS, Lee T, Shenoy S, Yevzlin AS, Abreo K, *et al*. KDOQI clinical practice guideline for vascular access: 2019 update. Am J Kidney Dis 2020; 75(suppl 2):S1–S164.

3 Chiu CH, Wang CY, Moi SH, Wu CH, Yang CH, Chen JB. Comparison of tunneled central venous catheters and native arteriovenous fistulae by evaluating the mortality and morbidity of patients with prevalent hemodialysis. J Formos Med Assoc 2019; 118:807–814.

4 Castro V, Farber A, Zhang Y, Dicken Q, Mendez L, Levin SR, *et al*. Reasons for long-term tunneled dialysis catheter use and associated morbidity. J Vasc Surg 2021; 73:588–592.

5 Hilleman D, Campbell J. Efficacy, safety, and cost of thrombolytic agents for the management of dysfunctional hemodialysis catheters: a systematic review. Pharmacotherapy 2011; 31:1031–1040.

6 Hemmelgarn BR, Moist LM, Lok CE, Tonelli M, Manns BJ, Holden RM, *et al*. Prevention of Dialysis Catheter Lumen Occlusion with rt-PA versus Heparin Study Group. Prevention of dialysis catheter malfunction with recombinant tissue plasminogen activator. N Engl J Med 2011; 364:303–312.

7 Ponikvar R, Buturovic-Ponikvar J. Temporary hemodialysis catheters as a long term vascular access in chronic hemodialysis patients. Ther Apher Dial 2005; 9:250–253.

8 Besarab A, Pandey R. Catheter management in hemodialysis patients: delivering adequate flow. Clin J Am Soc Nephrol 2011; 6:227–234.

9 Grossberg JA, Rebello LC, Haussen DC, Bouslama M, Bowen M, Barreira CM, *et al*. Beyond large vessel occlusion strokes: distal occlusion thrombectomy. Stroke 2018; 49:1662–1668.

10 Konstantinides SV, Meyer G, Becattini C, Bueno H, Geersing GJ, Harjola VP, *et al*. The Task Force for the diagnosis and management of acute pulmonary embolism of the European Society of Cardiology (ESC). 2019 ESC Guidelines for the diagnosis and management of acute pulmonary embolism developed in collaboration with the European Respiratory Society (ERS): The Task Force for the diagnosis and management of acute pulmonary embolism of the European Society of Cardiology (ESC). Eur Respir J 2019; 54:1901647.

11 Vats HS. Complications of catheters: tunneled and non-tunneled, advances in chronic kidney disease. Adv Chronic Kidney Dis 2012; 19:188–194.