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ORIGINAL ARTICLE / ОРИГИНАЛНИ РАД

# Tissue plasminogen activator for dysfunctional tunneled vascular catheters for hemodialysis – single center experience

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**SUMMARY**

**Introduction/Objective** Thrombosis of hemodialysis catheters is one of the major complications, which leads to catheter dysfunction. Although tissue plasminogen activator has been proven to be effective in reestablishing blood flow rate through dysfunctional catheters, clinical data in Serbia are missing. The objective of the study was to analyze tissue plasminogen activator efficacy in reestablishing blood flow rate and the influence on catheter survival.

**Methods** The study included 53 tunneled catheters from 32 patients on hemodialysis. After catheter dysfunction was established, 580,000 units of tissue plasminogen activator was applied into each catheter lumen for about two hours before hemodialysis. The criteria for success was blood flow rate on the next hemodialysis – over 200 mL/minute was considered to be complete success, 180–200 mL/minute partial success, and under 180 mL/minute was considered a failure.

**Results** Out of 53, 25 catheters (47%) had dysfunction with an incidence of 3.8/1,000 catheter days. Catheters placed in femoral veins, "after-first" catheters, catheters with infection, and catheters in older patients had higher risk for dysfunction. Multivariate logistic regression analysis confirmed that only older age was significantly related to catheter dysfunction. Of the total of 50 applications of tissue plasminogen activator, 35 (70%) were successful, seven procedures (14%) were partially successful and eight (16%) dysfunctional catheters failed to respond to therapy. Six-, 12- and 24-month survival was 87%, 81%, and 20%, respectively, for catheters without dysfunction, and 71%, 47.5%, and 12%, respectively, for catheters with dysfunction.

**Conclusion** Tissue plasminogen activator dosing is noninvasive, efficient, and safe in reestablishing blood flow rate through dysfunctional catheters, thus prolonging catheters life and sparing patients from additional vascular procedures.

**Keywords:** hemodialysis; tunneled vascular catheters; catheter thrombosis; tissue plasminogen activator

## INTRODUCTION

Adequate vascular access is crucial for successful hemodialysis (HD) treatment. Ideal access provides adequate blood flow rate (BFR) during an HD session and an adequate dialysis dose. Also, it has a few complications in the long term [1]. According to Vascular Access Society guidelines, arterial-venous fistula (AVF) is considered the best vascular access, based on its longevity and the rarity of complications [2]. If blood vessels were inadequate for the creation of AVF, then the creation of arterial-venous graft (AVG) should be considered. AVG provides adequate BFR during an HD session, but complications such as infection and thrombosis are more frequent comparing to AVF [1].

Tunneled vascular catheters (TVC) are used in patients whose blood vessels are exhausted for the creation of AVF or AVG, in patients with severe peripheral vascular disease, and in those with short life expectancy [3]. Although they are ready for use right after the insertion, providing satisfactory BFR, the rate of complications is discouraging. In regard to complications, femoral veins are considered to be the worst position for catheter placement, especially compared to the right internal jugular vein, which is usually recommended [4]. According to studies, six-month survival of TVC is 60%, and one-year survival is 40% [5].

National Kidney Foundation Dialysis Outcomes and Quality Initiative defined catheter dysfunction as a failure to attain and maintain an extracorporeal BFR of 300 mL/minute or greater at a prepump arterial pressure lower than -250 mmHg, and increased venous resistance (> 250 mmHg) [1]. Catheter dysfunction is also considered if Kt/V is lower than 1.2, or if urea reduction rate (URR) is < 65%, without extending HD.

The most common complications related to the catheters are infection and thrombosis [6]. They usually require catheter replacement, which is an invasive procedure accompanied by many complications: pneumothorax (0.2% if the internal jugular vein is punctured, and 3.1% if the subclavian vein is punctured), artery puncture (9.4% in attempt to puncture the internal jugular vein, 4.9% for the subclavian

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vein, and 15% for the femoral vein), bleeding (3%), hemothorax ( 0.6%), arrhythmias (0.9%), malposition (1%), perforation of the right atrium [7, 8].

Risk factors for thrombosis may be related to the catheter or to the patient. Catheter duration and catheter lumen width are directly proportional to thrombosis rate [9]. Risk factors related to patients are heart failure, infections, and malignant tumors [10]. In order to prevent catheter thrombosis, anticoagulants (heparin or sodium citrate) are placed in catheter lumens between two HD sessions. Theoretically, tissue plasminogen activator (TPA) can be used for the prevention of catheter thrombosis, but it is still debatable considering the cost–benefit relation. Therefore, it is mostly used for the treatment of acute catheter thrombosis [11, 12]. TPA translates plasminogen to plasmin, which is a powerful proteolytic enzyme that degrades fibrin fibers and other coagulation proteins [13].

According to some literature data, local application of TPA in catheter lumens is safe and efficient [14]. In clinical practice, there are no guidelines for the optimal dose of TPA. In a retrospective cohort study, Yaseen et al. [15] compared efficacy of 1 mg of TPA and 2 mg of TPA per catheter lumen and results revealed that catheter survival was better after using 2 mg of TPA per catheter lumen. Also, it has been shown that the risk for catheter replacement due to non-resolved obstruction is 2.75 times greater after using 1 mg of TPA per catheter lumen. Macrae et al. [16] compared one hour to 48 hours TPA dwell, and there was no statistically significant difference between the short and long TPA dwell groups for catheter patency at the subsequent HD run (76.9% *vs*. 79.4%) or at two weeks (42.3% *vs*. 52.9%).

The objective of this prospective study was to analyze the efficacy and safety of TPA application on reestablishing blood flow through dysfunctional TVC, and to confirm the influence of TPA on catheter survival.

## METHODS

### Patients and catheters

This prospective study examined all TVC (Hickman, Bard, Salt Lake City, UT) placed between March 1, 2012 and December 1, 2014 in patients treated with chronic HD in Clinical Department for Renal Diseases, Zvezdara University Medical Center, Belgrade.

A database was constructed based on the patient's medical documentation. All patients were dialyzed three times weekly, for four hours. Patients were followed up from the day of catheter insertion to the day of catheter removal, death, or the end of the study period. The catheters were inserted by vascular surgeon under local anesthesia, without radioscopic or ultrasound guidance. After catheter placement, X-ray was performed to ensure adequate catheter position. Only catheters that were functional at least three consecutive HD after insertion were analyzed.

Some patients had more than one catheter, since catheters were replaced due to the complications. Second and following catheters were simply called "after-first" catheters. Most of the patients had AVF and/or AVG and/or peritoneal dialysis (PD) before catheter placement.

According to the unit protocol, catheter dysfunction was defined as the difficulty in infusing or withdrawing blood from their lumens. Risk factors for catheter dysfunction were evaluated, including sex, age, length of dialysis, comorbidities (hypertension and diabetes mellitus), associated infections, use of antiplatelet and oral anticoagulant therapy (OACT), laboratory analyses (albumin and hemoglobin level), and catheter location.

### TPA application

Due to acute catheter dysfunction, patients received 580,000 units (1 mg) of TPA into each catheter lumen. TPA was diluted with saline in final concentration that fits every catheter lumen. Dwell time was two hours before HD.

The criterion for success was BFR on subsequent HD session was as follows: over 200 mL/minute was considered to be complete success, 180–200 mL/minute partial success, and under 180 mL/minute was considered failure of therapy. Criteria for catheter function/dysfunction are not clearly stated by current guidelines or literature data, since dialysis adequacy is the main criteria for catheter replacement. Therefore, decision about catheter dysfunction and removal is usually brought according to BFR, dialysis adequacy and patient's residual renal function. Still, it is desirable to achieve BFR of more than 200 mL/minute for adequate HD. If BFR is less than 200 mL/minute (180–200 mL/minute), adequate dialysis could still be achieved by selection of dialyzer of higher surface area and by prolonging dialysis time, particularly if the patient has preserved residual renal function. Therefore, we designated such flow rate as partial success and it was still functional catheter, with no need for removal. However, with BFR less than 180 mL/minute, adequate HD can hardly be achieved and therefore we assumed these catheters failed (dysfunctional).

Since catheter thrombosis is the most common cause of catheter dysfunction, we performed X-ray diagnostic procedures to determine the etiology of dysfunction only if the second dose of TPA failed to provide BFR through catheter.

### Statistical analysis

SPSS Version 15.0 (SPSS Inc. Chicago, IL, USA) was used to analyze the data. Descriptive analysis was applied to study the characteristics of the study population and of the catheters. Student's t-test was performed for intergroup comparison for variables with normal distribution. For variables without normal distribution, differences between the groups was analyzed with the Mann–Whitney test. Kaplan–Meier curves were constructed for catheter survival. We censored for events that led to catheter removal such as catheter bacteremia, the transition to an AVF or the start of PD, and patient death. Logistic regression analysis was applied to study the influence of covariates on the incidence of catheter dysfunction. Independent variables were age, sex, comorbidities (hypertension and diabetes mellitus), associated infections, OACT, antiplatelet therapy, hemoglobin and albumin level,

length of dialysis, and catheter location. The dependent variable was catheter dysfunction (0 for catheters without dysfunction and 1 for catheters with dysfunction). Statistical significance for all comparisons was set at $p \leq 0.05$.

## RESULTS

### Patient characteristics

The median length of the follow-up was seven months (range 1–32 months). Study included 16 men (50%) and 16 women (50%) of the average age of 62 ± 14 years (Table 1). Most of the patients had hypertension (81%), and 22% of them had diabetes mellitus. Only five patients (16%) started dialysis with TVC, while the others were on dialysis for 38 ± 52 months before they had their tunneled catheters placed. Most of the patients used AVF before catheter (78%), 37.5% had AVG, and 31% were treated with PD.

**Table 1.** Data on the patients and catheters

| Parameter | Patients, n = 32 |
|---|---|
| Male sex, n (%) | 16 (50) |
| Age (X ± SD) | 62 ± 14 (min. 30, max. 80) |
| Diabetes mellitus, n (%) | 7 (22) |
| Hypertension, n (%) | 26 (81) |
| Dialysis duration before catheter (months), (X ± SD) | 38 ± 52 (min. 1, max. 196) |
| Previous access for dialysis:<br>– patients with AVF, n (%)<br>– patients with AVG, n (%)<br>– switch from PD, n (%)<br>– catheter as the first access, n (%) | <br>25 (78)<br>12 (37.5)<br>10 (31)<br>5 (16) |
| Hemoglobin concentration (≥ 95 g/L), n (%) | 22 (69) |
| Albumin concentration (< 35 g/L), n (%) | 9 (28) |
| Usage of antiplatelet therapy, n (%) | 16 (50) |
| Usage of OACT, n (%) | 4 (12.5) |
| Overall number of catheters | 53 |
| Number of dysfunctional catheters, n (%) | 25 (47) |
| Time to first dysfunction (days), median (IQR)<br>– first catheters<br>– after-first catheters | <br>235 (304)<br>100 (151) |
| Incidence of dysfunction per 1,000 catheter days | 3.8/1,000 catheter days |
| TPA application per dysfunctional catheter (X ± SD) | 2 ± 1.8 (min. 1, max. 9) |
| Number of catheter-related bacteremia, n (%) | 16 (30) |

AVF – arterial-venous fistula; AVG – arterial-venous graft; PD – peritoneal dialysis; OACT – oral anticoagulant therapy; TPA – tissue plasminogen activator; IQR – interquartile range

Twenty-two patients (69%) had a desirable hemoglobin level, but almost one third of them had albumin concentration below the lower limit. Half of them were using antiplatelet therapy, and 12.5% were using OACT.

During the study, 53 catheters were placed in 32 patients. The maximal number of catheters received by a single patient over the study period was four. Out of 53 catheters, 25 (47%) had dysfunction which required the use of TPA once or repeatedly. Incidence of dysfunction was 3.8/1,000 catheter days.

Time to the first catheter dysfunction varied 6–670 days (median being 110 days). We investigated if there was difference in time to first dysfunction between the first catheters and the after-first catheters. Since data were nonparametric, we performed the Mann–Whitney test and confirmed that there was statistically significant difference between the first and the after-first catheters regarding the time to the first dysfunction ($p = 0.043$).

The number of TPA applications per dysfunctional catheter was 2 ± 1.8 (min. 1, max. 9). Sixteen catheters (30%) had catheter-related bacteremia, but there was no significant difference in catheter dysfunction between catheters with or without infection ($p = 0.14$).

Table 2 presents the success of the TPA procedure. In 25 dysfunctional catheters, 50 TPA applications were performed. In 35 applications (70%), the use of TPA was followed by adequate HD session. In seven applications (14%), partial success was achieved, and eight (16%) dysfunctional catheters failed to respond to therapy with TPA. We didn't find any statistically significant difference in success between the first, the second, and subsequent TPA application per catheter ($p = 0.9$).

**Table 2.** Number of successful tissue plasminogen activator procedures (success, partial success and failure)

| Number of TPA procedures per catheter | Immediate success of TPA procedure | | |
|---|---|---|---|
| | Success (BFR > 200 mL/minute) n = 35 | Partial success (BFR 180–200 mL/minute) n = 7 | Failure (BFR < 180 mL/minute) n = 8 |
| First | 18 (72%) | 3 (12%) | 4 (16%) |
| Second | 8 (66.7%) | 2 (16.7%) | 2 (16.7%) |
| Subsequent (3–9) | 9 (69.2%) | 2 (15.4%) | 2 (15.4%) |

BFR – blood flow rate; TPA – tissue plasminogen activator

Also, there was no difference in success rate of the TPA procedure between the first and the after-first catheters ($p = 0.57$).

### Catheter survival

As a prediction, if catheters had been removed after the first dysfunction without TPA therapy, one-year survival of dysfunctional catheters would have been only 12% (Figure 1). Figure 2 shows survival curves for the catheters with and without dysfunction and TPA intervention. Six-, 12- and 24-month survival was 87%, 81%, and 20%, respectively, for catheters without dysfunction, and 71%, 47.5%, and 12%, respectively, for catheters with dysfunction in which TPA therapy was applied. Log rank test was performed and a statistical difference between two Kaplan–Meier curves was not confirmed ($p = 0.1$).

In nine dysfunctional catheters (36%) after one use of TPA, catheters continued to function without any need for additional TPA procedures. In three catheters (12%) after the second unsuccessful dose of TPA, diagnostic procedures were performed and an X-ray revealed secondary catheter malposition, which required catheter replacement.

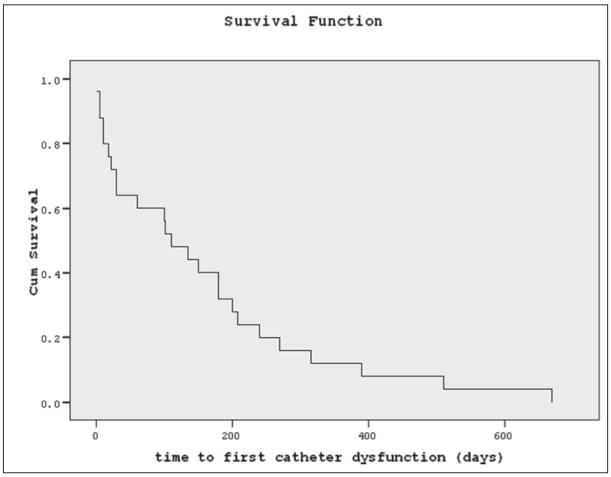


**Figure 1.** Prediction of overall catheter survival without tissue plasminogen activator procedure (Kaplan–Meier survival curve)

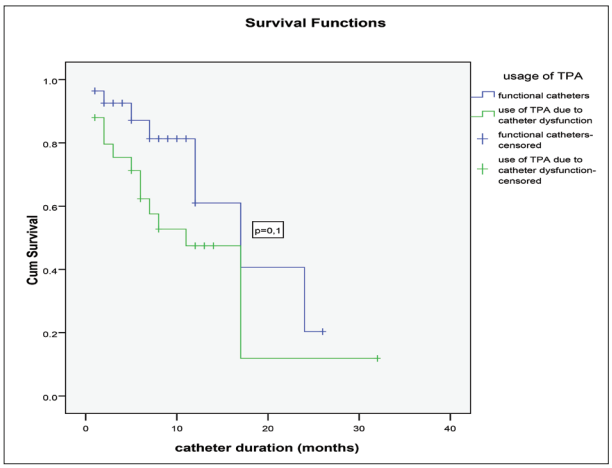


**Figure 2.** Kaplan–Meier survival analysis for functional and dysfunctional catheters treated with tissue plasminogen activator

### Risk factors for catheter dysfunction

Table 3 shows the results of multivariate logistics regression analysis. Only older age was significantly related to catheter dysfunction, but not the use of antiplatelet and OAC drugs, sex, comorbidities (hypertension, diabetes mellitus), laboratory analyses (albumin and hemoglobin level), and the length of HD. Femoral location of the catheter had three times higher risk for developing dysfunction compared to jugular and subclavian localization, but this difference did not reach statistical significance. Concomitant bacteremia increases the risk for dysfunction two-fold, and the after-first catheters are at 1.5 higher risk compared to the first catheters, both without statistical significance.

**Table 3.** Variables associated with dysfunction of tunneled vascular catheters

| Covariates | B | Exp (B) | p | 95% CI |
|---|---|---|---|---|
| Age | 0.045 | 1.046 | 0.036 | 0.003–1.091 |
| Association with infection | 0.752 | 2.122 | 0.269 | 0.559–8.058 |
| Femoral veins | 1.093 | 2.982 | 0.164 | 0.640–13.892 |
| After-first catheters | 0.407 | 1.503 | 0.548 | 0.398–5.665 |

## DISCUSSION

This study confirmed that 25 (47%) out of 53 examined catheters had dysfunction that required the use of TPA, with the incidence of dysfunction of 3.8/1,000 catheter days. The literature data revealed lower incidence; Develter et al. [17] described 1.94 dysfunctions per 1,000 catheter days, while Lee et al. [18] found three dysfunctions per 1,000 catheter days, and the difference could be explained by different patient populations – our patients were older and had higher comorbidity, including diabetes mellitus.

By using logistic regression analysis, we confirmed that age was the only significant risk factor for catheter dysfunction. Timsit et al. [19] also showed that older patients are at a higher risk for developing catheter thrombosis. This might be due to many comorbidities and damaged blood vessels that are more frequent in the elderly, which makes them prone to thrombosis.

The relationship between catheter-related bacteremia and thrombosis has been proven by literature data [19, 20]. It is still debatable whether infection promotes thrombosis or vice versa. One of the possible explanations could be that the fibrin sheath surrounding catheters increases bacterial adherence [21]. Vaudaux et al. [10] in their study suggested that host factors, such as fibrin, fibronectin, and fibrinogen, may have a significant role in staphylococcal adherence, colonization, and infection by interacting with intravascular catheters. According to our data, only 30% of dysfunctional catheters were associated with bacteremia. Therefore, it is difficult to confirm the clear relationship between two events.

As shown in previous studies, femoral approach is associated with higher risk of thrombotic complications, which is also proved by our study, although without statistical significance. The most striking results were shown by Merrer et al. [22], who compared subclavian and femoral approach, where femoral approach proved to be the most unfavorable one (1.9% *vs.* 21%).

A systematic review was performed to evaluate studies that examined the efficacy and safety of thrombolytic therapy in dysfunctional HD catheters [23]. The success rate was higher with reteplase (88%), followed by TPA (81%), and tenecteplase (41%).

In our study, the use of TPA proved to be successful in re-establishing BFR in subsequent HD in 70% of the procedures. These results are in compliance with the study by Ponce et al. [24], according to which adequate BFR on the following HD session was achieved in 77% of dysfunctional catheters after one TPA dose, in 10% after the second dose, and only 13% of catheters failed to respond to treatment. On the other hand, Little and Walshe [25] showed that the cumulative gain of repeated use of TPA in an attempt at thrombolysis is small. Authors stated that if the TPA is required more than once, it might be that the catheter has been structurally altered.

Since 1993, the use of TVC for HD has increased from less than 10% to more than 30%, as revealed by the US Renal Data System [26]. Data for Serbia in 2012 have shown that 89% of the prevalent patients used AVF as the

vascular access for HD and 3.1% used AVG. The percentage of prevalent patients with TVC was 3.5%. During 2012, 88% of the patients started HD with AVF, 4% with AVG, and 7.8% with TVC, thus showing a growing trend [27].

In our study, one-year survival of dysfunctional catheters treated with TPA was 47.5%. As a prediction, if catheters had been replaced after the first dysfunction, one-year survival would have been only 12%, as revealed by the Kaplan–Meier analysis. Log rank test did not confirm any statistically significant difference in survival between functional and dysfunctional catheters, in which TPA therapy was applied. This finding proves that TPA is successful in prolonging dysfunctional catheters life and saving patients from additional interventions, since the most of them have no alternative to another vascular approach.

In our study, there were no adverse effects of the TPA therapy. Previously mentioned systematic review also reported extremely rare adverse effects of thrombolytic therapy, most likely due to limited systemic exposure to TPA [23].

There are some limitations to our study. In addition to the small study population and the number of catheters, etiology of catheter dysfunction was examined after failure of the second dose of TPA, so secondary malposition was overlooked in three catheters. Therapeutic success of TPA was evaluated by the BFR, but not with color Doppler imaging and dialysis adequacy (Kt/V) which could be a useful diagnostic tool in case of recirculation over the catheter.

## CONCLUSION

This prospective single-center study provides data on permanent tunneled vascular catheters for HD with an acceptable dysfunction rate (3.8/1,000 catheter days). If dysfunction occurs, TPA is proven to be efficient, safe, easy to perform, and without significant disruption to the dialysis schedule. It has also shown that TPA extends catheter longevity in patients with exhausted other alternatives for dialysis.

**Conflict of interest:** None declared.

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# Ткивни активатор плазминогена код дисфункционалних тунелизованих васкуларних катетера за хемодијализу – искуство једног центра

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**САЖЕТАК**

**Увод/Циљ** Тромбоза катетера за хемодијализу је једна од најчешћих компликација која доводи до дисфункције катетера. Ткивни активатор плазминогена се показао ефикасним у решавању ове компликације, али клинички подаци у Србији недостају.

Циљ рада је испитивање ефикасности ткивног активатора плазминогена у поновном успостављању протока крви преко дисфункционалног катетера и утицаја на век трајања катетера.

**Методе** У студију је укључено 53 тунелизованих катетера код 32 болесника на хемодијализи. По утврђивању дисфункције, примењено је по 580.000 јединица ткивног активатора плазминогена у сваки лумен катетера два сата пре хемодијализе. Критеријум за терапијски успех је био проток крви на наредној хемодијализи: преко 200 *ml/min.* се сматрало комплетним успехом, од 180–200 *ml/min.* делимичним успехом и испод 180 *ml/min.* неуспехом.

**Резултати** Од 53 испитивана катетера, 25 (47%) њих је имало дисфункцију са учесталошћу 3,8/1000 катетер дана. Већи ризик за дисфункцију су имали катетери пласирани у феморалним венама, „наредни" катетери, катетери са придруженом инфекцијом и катетери код старијих болесника. Мултиваријантна регресиона анализа је потврдила да катетери код старијих болесника имају статистички значајно већи ризик за дисфункцију. Од укупно 50 примена ткивног активатора плазминогена било је 35 (70%) успешних, седам (14%) делимично успешних и осам (16%) неуспешних покушаја остваривања адекватног протока крви преко дисфункционалног катетера. У групи катетера који нису имали дисфункцију, након шест, 12 и 24 месеца проценат функционалних катетера је износио 87%, 81% и 20%, док је у групи катетера са дисфункцијом тај проценат био 71%, 47,5% и 12%.

**Закључак** Примена ткивног активатора плазминогена је неинвазивна, ефикасна и безбедна за поновно успостављање протока крви преко дисфункционалног катетера, уз продужетак века трајања катетера и поштеду болесника од додатних васкуларних интервенција.

**Кључне речи:** хемодијализа; тунелизовани васкуларни катетери; тромбоза катетера; ткивни активатор плазминогена