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

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

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

SUMMARY

Introduction/Objective Thrombosis of hemodialysis catheters is one of the major complication which leads to catheter dysfunction. Although tissue plasminogen activator has been proven to be effective for reestablishing blood flow rate through dysfunctional catheters, clinical data in Serbia are missing.

The aim of the study is to analyze tissue plasminogen activator efficacy in reestablishing blood flow rate and the influence on catheter survival.

Methods 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 next hemodialysis: over 200ml/min was considered complete success; 180-200ml/min as partial success and under 180ml/min as a failure.

Results Out of 53, 25 catheters (47%) had dysfunction with incidence of 3.8/1000 catheter days. Higher risk for dysfunction had catheters placed in femoral veins, “after first” catheters, catheters with infection and catheters in older patients. Multivariate logistics regression analysis confirmed that only older age was significantly related to catheter dysfunction. All together 50 tissue plasminogen activator were applied, and 35 (70%) was successful, 7 procedures (14%) were partially successful and 8 (16%) dysfunctional catheters failed to respond to therapy. Six, 12 and 24 months survival were 87%, 81% and 20% for catheters without dysfunction and 71%, 47.5% and 12% 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

САЖЕТАК

Увод/Циљ Тромбоза катетера за хемодијализу је једна од најчешћих компликација која води дисфункцији 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 утицај на век трајања катетера.

Методе У студију је укључено 53 тунелизованих катетера код 32 болесника на хемодијализи. По утврдјивању 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 200ml/min је сматран комплетиним успехом, од 180-200ml/min делимичним успехом и испод 180ml/min неуспехом.

Резултати Од 53 испитиваних катетера, 25 (47%) 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 35 (70%) је било успешних, 7 (14%) делимично успешних и 8 (16%) неуспешних покушаја остваривања адекватног протока крви преко дисфункционалног катетера. У групи катетера који нису имали дисфункцију, након 6, 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

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INTRODUCTION

Adequate vascular access is crucial for successful hemodialysis (HD) treatment. Ideal access provides adequate blood flow rate (BFR) during HD session and adequate dialysis dose. Also, it has a few complications in long term [1]. According to Vascular Access Society guideline [2], arterial-venous fistula (AVF) is considered the best vascular access based on longevity and rare complications. If blood vessels were inadequate for AVF creation, than creation of arterial-venous graft (AVG) should be considered. AVG provides adequate BFR during 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 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 insertion, providing satisfactory BFR, rate of complications is discouraging. In regard to complications, femoral veins are considered as the worst position for catheter placement, especially compared to the right internal jugular vein which is usually recommended [4]. According to studies, six months survival of TVC is 60%, and one year survival is 40% [5].

National Kidney Foundation’s Dialysis Outcome and Quality Initiative (KDOQI) [1] defined catheter dysfunction as failure to attain and maintain an extracorporeal BFR of 300 mL/min or greater at a prepump arterial pressure more negative than –250 mm Hg, and increased venous resistance (>250mmHg). 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 invasive procedure accompanied by many complications: pneumothorax (0.2% if internal jugular vein is punctured, and 3.1% if subclavian vein is punctured), artery puncture (9.4% in attempt to puncture internal jugular vein, 4.9% for subclavian vein, and 15% for femoral vein), bleeding (3%), hemothorax (0.6%), arrhythmias (0.9%), malposition (1%), perforation of 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 prevention of catheter thrombosis, but it is still debatable considering cost-benefit. Therefore it is mostly used for treatment

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of acute catheter thrombosis [11, 12]. TPA translates plasminogen to plasmin, which is 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 optimal dose of TPA. In retrospective, cohort study Yaseen et al. [15] compared efficacy of 1mg TPA and 2mg TPA per catheter lumen and results revealed that catheter survival was better after using 2mg of TPA per catheter lumen. Also it has been shown that the risk for catheter replacement due to non resolved obstruction is 2,75 time greater after using 1mg of TPA per catheter lumen. Macrae et al. [16] compared one hour to 48h TPA dwell, and there was no statistical 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 2 weeks (42.3% vs. 52.9%).

The aim 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 4 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: gender, age, length of dialysis, comorbidities (hypertension and diabetes mellitus), associated

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infections, usage 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 (1mg) 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: over 200ml/min complete success, 180-200ml/min partial success and under 180ml/min 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/min for adequate HD. If BFR is less than 200 ml/min (180-200 ml/min), adequate dialysis could still be achieved by selection of dialyser of higher surface area and by prolonging dialysis time, particularly if 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, if BFR is less than 180 ml/min, we can hardly achieve adequate HD and therefore we assumed these catheters as failed (dysfunctional).

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

Statistical analysis

The SPSS program version 15.0 was used to analyze the data. Descriptive analysis was applied to study the characteristics of the study population and of the catheters. For intergroup comparison for variables with normal distribution, Students t test was performed. For variables without normal distribution difference between groups was analyzed with Mann Whitney test. Kaplan–Meier curves were constructed for catheters 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's death. Logistic regression analysis was applied to study the influence of covariates on the incidence of catheter dysfunction. Independent variables were: age, gender, comorbidities (hypertension and diabetes mellitus), associated infections, OACT, antiplatelet therapy, hemoglobin and albumin level, length of

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dialysis and catheter location. Dependent variable was catheter dysfunction (0 for catheters without dysfunction and 1 for catheters with dysfunction). For all comparisons „$p \leq 0.05$“ was statistical significant.

RESULTS

Patients' characteristics

Median length of follow-up was 7 months (range, 1-32 months). Study included 16 men (50%) and 16 women (50%), average age 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, 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.

22 patients (69%) had desirable hemoglobin level, but almost third of them had albumin concentration below the lower limit. Half of them were using antiplatelet therapy, and 12.5% 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 usage of TPA once or repeatedly. Incidence of dysfunction was 3.8/1000 catheter days.

Time to first catheter dysfunction varied from 6-670 days (median 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 Mann Whitney test and confirmed that there was statistical significant difference between the first and the „after first“ catheters regarding the time to first dysfunction (p=0,043).

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 TPA procedure. In 25 dysfunctional catheters 50 TPA applications were performed. In 35 applications (70%) usage of TPA was followed by adequate HD session. In 7 applications (14%) partial success was achieved, and 8 (16%) dysfunctional catheters failed to respond to therapy with TPA. We didn't find statistical significant difference in success between the first, second and following TPA application per catheter (p=0,9).

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Also there was no difference in success rate of 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, than 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 months survival were 87%, 81% and 20% for catheters without dysfunction and 71%, 47.5% and 12% for catheters with dysfunction in which TPA therapy was applied . Log rank test was performed and 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 need for additional TPA procedures. In three catheters (12%) after second unsuccessful dose of TPA, diagnostic procedures were performed and X-ray revealed secondary catheter malposition, which required catheter replacement.

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, gender, comorbidities (hypertension, diabetes mellitus), laboratory analyses (albumin and hemoglobin level) and length of HD. Femoral location of the catheter had three times higher risk for developing dysfunction comparing with jugular and subclavian localization, but this difference did not reach statistical significance. Concomitant bacteremia increases the risk for dysfunction two times and the "after first" catheters are at 1.5 higher risk comparing to the first catheters, both without statistical significance.

DISCUSSION

This study confirmed that 25 (47%) out of 53 examined catheters had dysfunction which required usage of TPA with incidence of dysfunction of 3.8/1000 catheter days. Literature data revealed lower incidence; Develter et al. [17] described 1.94 dysfunctions/1000 catheter days, and Lee

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et al. [18] 3.0 dysfunctions/1000 catheter days and difference could be explain by different patients population. Namely, our patients were older and had higher comorbidity including diabetes mellitus.

By 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 higher risk for developing catheter thrombosis. This might be due to many comorbidities and damaged blood vessels that are more frequent in 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 fibrin sheath surrounding catheters [21] increases bacterial adherence. 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 previously shown in 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 (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 usage of TPA proved to be successful in re-establishing BFR in subsequent HD in 70% of procedure. These results are in compliance with the study of Ponce et al. [24] where adequate BFR on next HD session was achieved in 77% of dysfunctional catheters after one TPA dose, 10% after the second dose, and only 13% of catheters failed to respond to treatment. On the other hand Little et al. [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. TVC had 3.5% of prevalent patients. During 2012. 88% of patients started HD with AVF, 4% with AVG, and 7.8% with TVC thus showing growing trend [27].

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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 Kaplan Meier analysis. Log rank test didn't confirm statistical 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 for another vascular approach.

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

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

CONCLUSION

This prospective, single center study provides data of the permanent, tunneled vascular catheters for HD with an acceptable dysfunction rate (3,8/1000 catheter days). If dysfunction occurs, TPA is proven to be efficient, safe, easy to perform and without significant disruption to the dialysis schedule. It is also shown that TPA extends catheters longevity in patients with exhausted other alternatives for dialysis.

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Table 1. Data about patients and catheters

Patient parameters	**Patients n – 32**
Male gender (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: -patients with AVF (n, %) -patients with AVG (n, %) -switch from PD (n, %) -catheter as the first access (N, %)	 25 (78%) 12 (37.5%) 10 (31%) 5 (16%)
Hemoglobin concentration (≥95g/L), (n, %)	22 (69%)
Albumin concentration (<35g/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) -first catheters -“after first” catheters	 235 (304) 100 (151)
Incidence of dysfunction per 1000 catheter days	3.8 /1000catheter 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

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

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

BFR – blood flow rate; TPA – tissue plasminogen activator

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Table 3. Variables associated with dysfunction of tunneled vascular catheters

Covariates	B	Exp(B)	Significance	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

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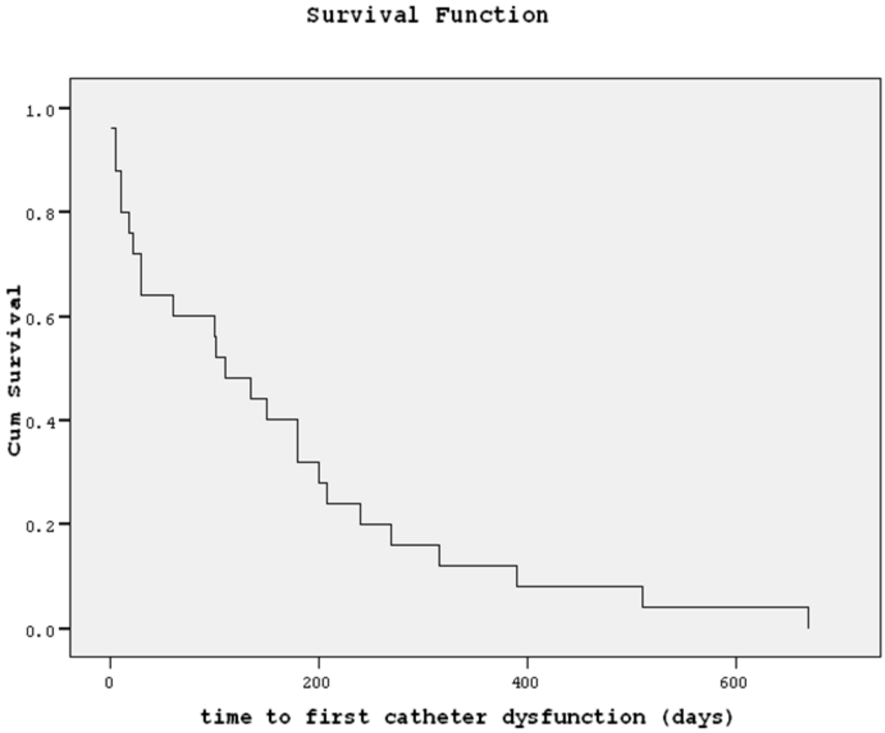

Figure 1. Prediction of overall catheter survival without tissue plasminogen activator procedure (Kaplan–Meier survival curve)

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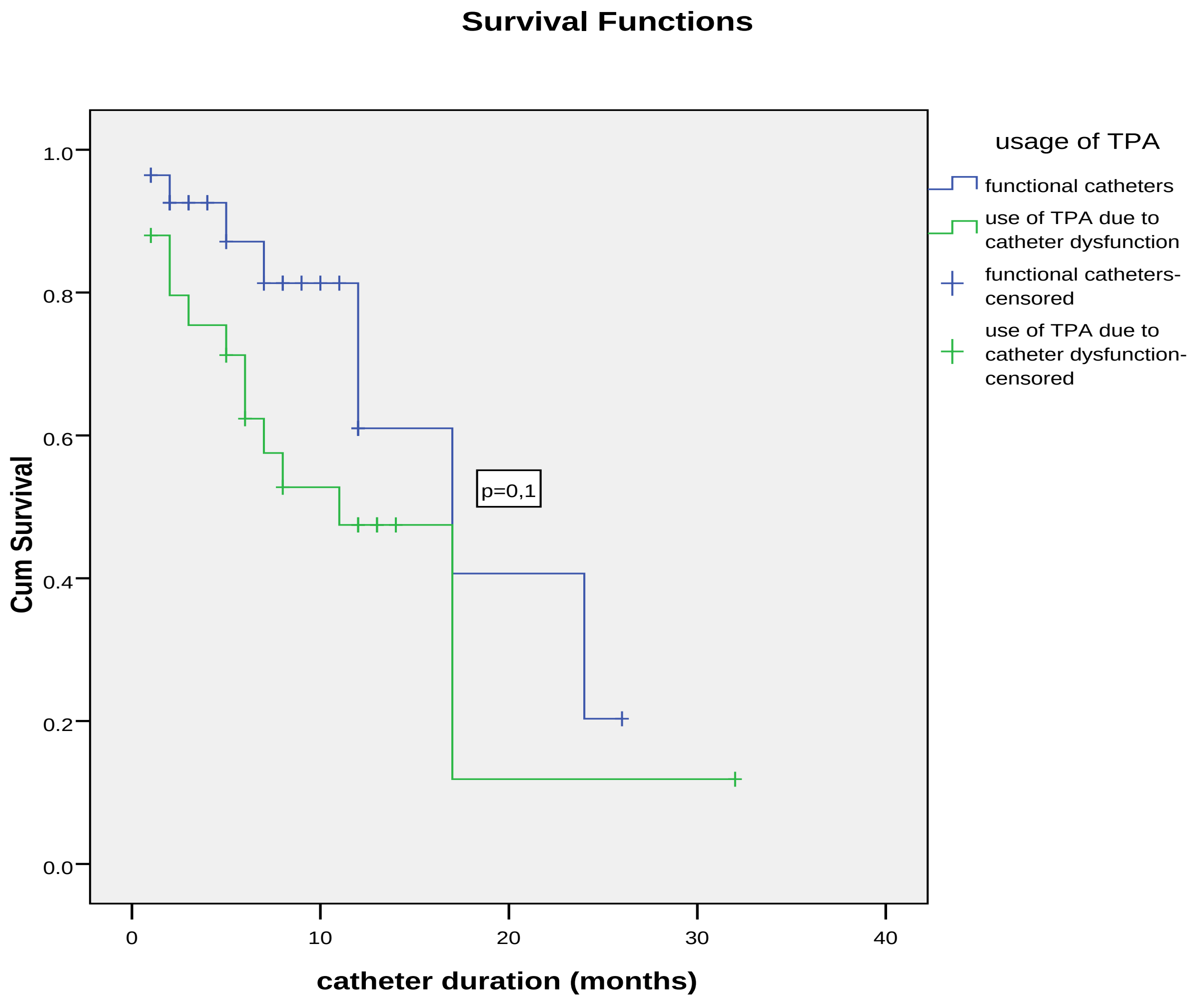

Figure 2. Kaplan–Meier survival analysis for functional and dysfunctional catheters treated with tissue plasminogen activator

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