10.5152/turkjnephrol.2019.3058

Original Article

Turkish Journal of Nephrology

Risk Factors for Catheter Related Central Venous Thrombosis in Hemodialysis Patients

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Abstract

Objective: Permanent catheters are used for vascular access in some patients undergoing hemodialysis (HD). Our aim in this study was to evaluate the risk factors of permanent catheter thrombosis and the necessity of anti-coagulant and anti-aggregation drugs.
Materials and Methods: In this retrospective study, 34 patients undergoing HD, with removed internal jugulary permanent catheters due to either thrombosis or maturation of operated arteriovenous fistulas, were included. Patients were divided into thrombotic and non-thrombotic, according to the catheter thrombosis status.
Results: The mean age was 66.3±15.4 years, and the follow-up period was 10.9±8.5 (1-29) months. Catheter thrombosis was found in 12 patients. Albumin and total protein levels were lower in the baseline thrombotic group (3.53±0.46 g/dL and 6.64±0.92g/dL, respectively)than in the non-thrombotic group (3.95±0.41 and 7.37±0.46g/dL, respectively).In the non-thrombotic group, hemoglobin, hematocrit higher, and platelet count were lower at the catheter removal time compared to the catheter insertion time (hemoglobin 11.45±1.25, hematocrit 35.61±4.51, and platelet count 193.82±66.32 versus hemoglobin 10.33±1.37g/dL, hematocrit 31.38±3.79% and platelet count 231.77±71.7x103/uL, respectively), but in the thrombotic group, the ferritin levels significantly increased from 541.3±574.8ng/mL at the catheter insertion time to 745.1±406.5ng/mL at the catheter removal time.
Conclusion: Anti-coagulant and anti-aggregation drugs and renal failure etiology did nothave any effect on permanent catheter thrombosis, but the albumin and total protein levels were related to it. Increased levels of ferritin and C-reactive protein seem to emerge as the acute phase reactants associated with thrombosis.
Keywords: Permanent hemodialysis catheter, thrombosis, anti-coagulant drug usage

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Received: 08.11.2017 **Accepted:** 10.10.2018

Cite this article as: Mağden K, Toka B, Yıldırım İ, Yıldız G, Köktürk F, Çil C, et al. Hemodialysis Catheter Thrombosis. Turk J Nephrol 2019; 28(1): 43-7.

INTRODUCTION

For patients who require renal replacement therapy, a permanent hemodialysis (HD) catheter for the vascular access can be used as an alternative route until the peripheral arteriovenous vascular access is prepared or in patients with vascular access problems. Depending on the time of insertion, in these catheters used for HD, partial or complete blockage may occur in 30% to 60% of cases (1). Thrombosis that occurs in the lumen or at the end of the catheter may not be resolved by thrombolytics. In this case, the catheter should be removed carefully. In patients with chronic renal failure who require renal replacement therapy, arteriovenous fistula (AVF) or grafts are used, and they are suitable for long-term use. During the time required for operational AVF, patients can undergo HD with temporary or permanent catheters. When fistula cannot be opened in HD patients, catheters can also be used. Tunneled cuffed venous catheters are the method of choice for temporary access that lasts longer than 3 weeks. In addition, some patients who have exhausted all other access options require a permanent access via tunneled cuffed catheters (2). The most common late complications are catheter thrombosis, fibrin sheath, venous thrombosis,

and breakage of the catheter tip. Catheter thrombosis can be caused by intrinsic reasons, such as partial or complete blockage or as a result of stenosis or occlusion of the vein with thrombosis (3). Dysfunction due to thrombosis can cause an inadequate dialysis with a low Kt/V level and urea reduction rate (4, 5). To prevent intraluminal thrombosis, an initial strong saline wash and anti-coagulant locking between the two HD sessions should be performed. The effective and safe way is to lock with concentrated heparin. As an alternative, sodium citrate locking can be performed (6). When intraluminal thrombosis occurred in patients with chronic renal failure, urokinase and alteplase could be used (7). If the catheter transition is limited, thrombolytics should be administered. In case of catheter blockage, the catheter should be removed. Venous thrombosis may occur as a result of long-term catheterization. In this case, the catheter should be also removed.

In this study, we aimed to evaluate the presence of intraluminal thrombosis after the catheter removal, its frequency, and the necessity of anti-coagulant application in patients with operational AVF and with non-functioning permanent catheters.

MATERIALS AND METHODS

Patients admitted to the Clinic of Nephrology of the Bulent Ecevit University Hospital for the removal of an internal jugular permanent catheter in 2012 due to dysfunction or of a functional catheter due to maturation of operated AVF were included in this retrospective study. The procedures followed were in accordance with the ethical standards of the committee on human experimentation and the Declaration of Helsinki and its revisions.

Drug and medical history, ultrafiltration, post-dialysis body weight, equilibrated Kt/V, urea reduction rate, complete blood count, activated partial thromboplastin time (aPTT), prothrombin time (PTT), international normalized ratio (INR), C-reactive protein (CRP), and all the routine biochemical tests were recorded from patients charts at the time of catheter insertion (basal) and removal time (final). Patients were grouped as thrombotic and non-thrombotic, according to the catheter thrombosis status. The research was conducted with the approval number 2013-27-26/02 of Bülent Ecevit University Ethics Committee.

Statistical Analysis

Statistical analysis was performed using the The Statistical Package for the Social Sciences (SPSS) 18.0 software (SPSS Inc.; Chicago, IL, USA). Data distribution was determined using the Shapiro-Wilks test. Continuous variables were expressed as the mean±standard deviation, and categorical variables were expressed variables as the frequency and percentage. Continuous variables were compared using the independent samples t-test or the Mann–Whitney U test, and categorical variables were compared using Pearson's chi-square test or Fisher'sexact chi-square test for two groups. The paired t-test or Wilcoxon rank sum test was used to evaluate repeated measures for continuous variables. The McNemar test was used to compare repeated measures for categorical variables. A p-value less than 0.05 was considered to bestatistically significant for all tests.

Table 1. Baseline characteristics

		Thrombus Absent (n=22)	Thrombus Present (n=12)	p
Age		67.8±22.2	63.5±10.4	0.536
Gender (Male, %)		72.7	33.3	0.036
Ethiology of ESRD (%)	Diabetic	68.2	41.7	0.290
	Unknown	31.8	58.4	

ESRD: end-stagerenaldisease

Table 2. Drug usage in the groups

	Non-thrombotic Group (n, 22) Basal	Thrombotic Group (n, 12) Basal	p
Coumadin	22.7	8.3	0.282
Aspirin	68.2	66.7	0.374
Beta blocker	27.3	8.3	0.203
CCB	45.5	50.0	0.807
ACEI/ARB	18.2	0	0.123
Alpha blocker	18.2	16.7	0.915
ESA	45.5	66.7	0.249
Vitamin D	31.8	50.0	0.312
Calcium acetate/ carbonate	63.6	58.3	0.770
Sevelamer	13.6	25.0	0.422
Intravenous iron	59.1	83.3	0.158
Folic acid	31.8	50.0	0.362
Vitamin B 12	22.7	58.3	0.039
Polystyrenesulphonate	13.6	0	0.191
Essential amino acid	45.5	16.7	0.099
Blood transfusion	9.1	0	0.296

CCB: calcium-channelblocker; ACEI: angiotensin-convertingenzymeinhibitors; ARB: angiotensin receptor blockers; ESA: erythropoietin-stimulating agent.

RESULTS

Thirty-four patients (mean age 66.3±15.4 years [12-90]; 20 males) were included in the study. Permanent hemodialysis catheters were removed due to catheter thrombosis in 35.2% of cases and operational AVF in 64.8% of cases. Catheter thrombo-

Table 3. Laboratory Findings and Clinical Parameters

	Non-thrombotic Group (n, 22) Basal	Thrombotic Group (n, 12) Basal	p
Hemoglobin (g/dL)	10.33±1.37	10.48±1.64	0.783
Hematocrit (%)	31.38±3.79	31.68±4.88	0.843
Leukocyte (10^3/uL)	7.27±2.81	8.15±2.77	0.391
Platelet (10^3/uL)	231.77±71.7	227.75±55.68	0.867
BUN entry (mg/dL)	112.95±48.44	125.42±40.53	0.455
BUN out (mg/dL)	41.13±22.10	38.53±10.46	0.705
Cr entry(mg/dL)	5.49±2.23	6.70±2.02	0.170
Cr out (mg/dL)	2.42±1.10	2.62±0.76	0.597
Ultrafiltration (L)	2.40±1.00	2.04±1.17	0.376
Post-dialysis BW (kg)	65.43±12.50	63.85±18.46	0.770
EquilibratedKt/V	1.44±0.24	1.52±0.25	0.412
URR (%)	67.37±4.73	67.71±6.24	0.865
Serum iron (µg/dL)	58.75±33.18	51.44±18.02	0.549
Total protein (g/dL)	6.64±0.92	7.37±0.46	0.021
Albumin (g/dL)	3.53±0.46	3.95±0.41	0.013
ALT (U/L)	18.09±20.34	12.00±4.41	0.317
Sodium (mmol/L)	137.34±3.85	139.08±2.61	0.171
Potassium(mmol/L)	4.75±0.75	4.80±0.76	0,868
Calcium (mg/dL)	8.96±0.84	9.33±1.04	0.050
Phosphorus (mg/dL)	4.59±1.35	4.95±1.25	0.458
Iron saturation (%)	27.31±14.20	25.00±11.43	0.681
Ferritin (ng/mL)	486.92±381.57	541.33±574.80	0.774
PTH (pg/mL)	341.89±257.93	578.22±557.47	0.137
Uric acid (mg/dL)	6.50±1.90	6.45±1.38	0.952
ALP (U/L)	139.83±88.45	92.75±25.91	0.156
CRP (mg/dL)	20.95±20.06	18.12±13.94	0.735
aPTT(sec)	30.47±6.12	28.67±6.18	0.517
PT (sec)	14.25±2.88	15.26±4.14	0.500
INR	1.18±0.32	1.16±0.41	0.901

BUN: bloodureanitrogen; Cr: creatinine; BW: body weight; URR: ureareductionratio; ALT: alanintransferase; PTH: parathyroidhormone; ALP: alkaline phosphatase; CRP: C-reactive protein; aPTT: activatedpartialthromboplastin time; PT: prothrombintime; INR: internationalnormalizedratio

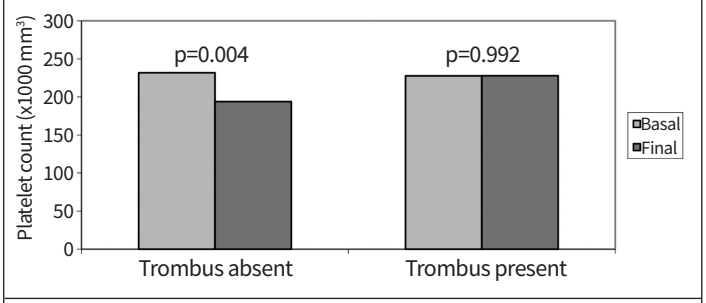

Figure 1. Platelet count

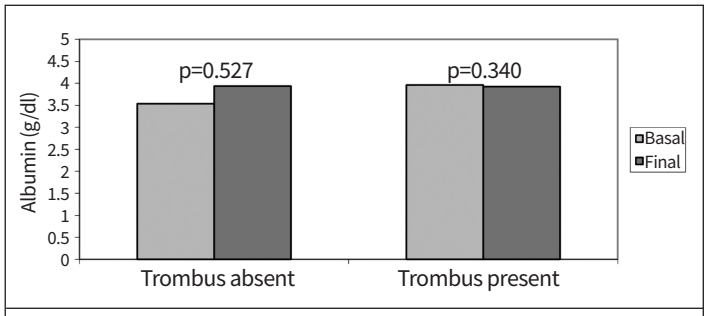

Figure 2. Albumin levels

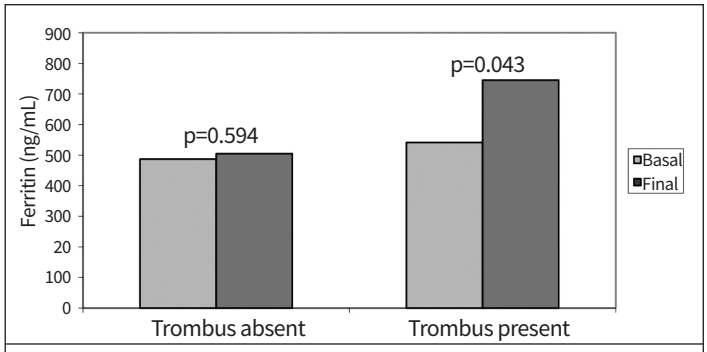

Figure 3. Ferritin levels

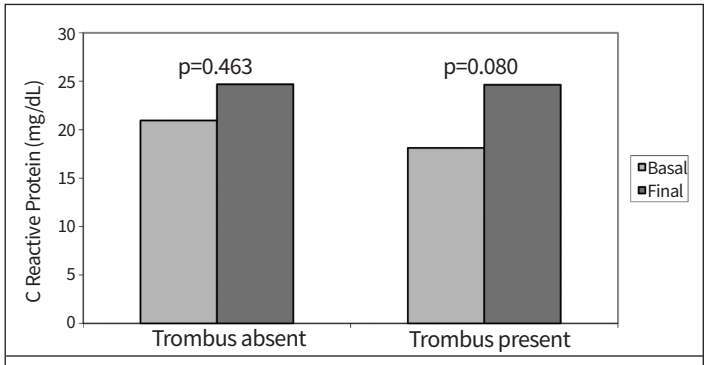

Figure 4. C-reactive protein

sis was found in 12 patients. There was a male predominance of 72.7%in the thrombosis-absent group (Table 1). There were no significant differences between the groups using coumadin, aspirin, anti-hypertensives, essential amino acids, vitamin D, and other multivitamin preparations (Table 2). The ratio of patients with diabetes mellitus was 41.7% in the thrombotic group and 68.2% in the non-thrombotic group (p>0.05). Albumin and total protein levels were lower in the baseline thrombotic group (3.53±0.46 g/dL and 6.64±0.92 g/dL, respectively) than in the non-thrombotic group (3.95±0.41 g/dL and 7.37±0.46g/dL, respectively; p>0.05; Table 2). In the non-thrombotic group, hemoglobin (Hb), hematocrit (Htc) higher and platelet count was lower at the catheter removal time compared to the catheter insertion time (11.45±1.25, 35.61±4.51, and 193.82±66.32 versus 10.33±1.37 g/dL, 31.38±3.79%, and 231.77±71.7x10^3/uL, respectively Figure 1). Albumin levels at the baseline and the cathe-

ter removal time in the thrombotic group were 3.95±0.41 g/dL and 3.92±0.40 g/dL, respectively, and 3.53±0.46 and 3.93±0.69 g/dL in the non-thrombotic group (p>0.05; Figure 2). In the thrombotic group, the ferritin levels increased significantly from 541.33±574.80 at the baseline to 745.10±406.53 ng/mL at the catheter removal time (Figure 3), which was significantly associated with an increase of serum CRP levels from 18.12±13.94 to 24.62±23.66 mg/dL, but did not reach statistical significance (Figure 4; Table 3). Prothrombin time levels at the baseline and the catheter removal time in the thrombotic group were 15.26±4.14 and 16.63±7.60 sec, respectively, and in the non-thrombotic group, they were 14.25±2.88 and 14.05±3.07 sec, respectively (p>0.05). The INR levels at the baseline and at the catheter removal time in the thrombotic group were 1.16±0.41 and 1.48±0.52, respectively, and in the non-thrombotic group, they were 1.18±0.32 and 1.26±0.52, respectively, (p>0.05; Table 3) for patients using coumadin.

DISCUSSION AND CONCLUSION

Thrombotic complications that cause catheter dysfunction are partial or complete blockage of the catheter with thrombosis, stenosis, or occlusion of the vein with thrombosis, and occurrence of an external fibrin sheath at the distal end of the catheter. The most common thrombotic complication is intraluminal catheter thrombosis (fibrin sleeve). This condition may cause intermittent or continuous catheter dysfunction (8, 9). If the catheter transition is limited, a thrombolytic agent should be administered. In case of catheter blockage, the catheter should be removed. In a previous study conducted by Oguzkurt et al. (9), it was found that there were thrombus formations on the vein wall present in 28% of patients after the catheter extraction. In our study, permanent hemodialysis catheters were removed due to catheter thrombosis or due tothe presence of operational AVF (35.2% and 64.8%, respectively). We found that catheter thrombosis was more frequent in women than in men, which may be related to sex hormones, and these results are similar to results of a previous study conducted by Feldman et al. (10). In different studies, it was found that diabetic patients were at a high risk for the development of thrombosis (11, 12) but in our study, an etiology of diabetes mellitus did not increase the risk of catheter thrombosis. In our study, the use of intravenous iron and an erythropoietin-stimulating agent (ESA) was more remarkable in the thrombotic group than in the non-thrombotic group. Andrew et al. (13) have reported that high hematocrit levels contribute to mortality and thrombosis in rats that were given ESA. In our study, we found that in the non-thrombotic group, Hb, Hct lower and platelet count were higher compared to the thrombotic group at the catheter insertion time. Prevention or minimizing of potential morbidity and mortality in HD patients using a permanent catheter and monitoring the catheter thrombus as a major clinical complication is essential (14). Antithrombotic therapy was shown to be effective after the formation of thrombus (15). Zellweger et al. (16) reported that the use of adequate anticoagulation therapy and aspirin intake prevent dysfunction and thrombosis in HD patients with a permanent tunneled catheter. Mandolfo et al. (17) explained that oral anti-coagulant therapy is not useful in primary prevention of thrombosis but before replacing the central venous catheters thrombolytic treatment followed by oral anticoagulants, aiming at an INR target between 2 and 3. Before oral anti-coagulant therapy, they suggest a careful evaluation of potential overall benefits and paying attention to concomitant antiplatelet therapy. Ervo et al. (18) emphasized that several episodes of thrombosis (6% of dialyses) occurred, which required urokinase treatment and catheter replacement in 12 patients (9.6%), and in their experience, a higher rate of malfunctioning catheters was in the group that did not receive anticoagulation therapy. Zhang et al. (19) pointed out that catheter thrombosis is the most common complication and that urokinase infusion followed by anticoagulants can significantly prolong the catheter life-time. There was no statistically significant correlation between the presences of thrombus formation in the coumadin group. The prevalence of warfarin use among HD patients is reported to range between 8% and 25%, with up to 70% of patient spresumably taking the drug for the prevention of vascular access thrombosis, despite the lack of prospective data to support its use for this (or any other) indication (20, 21).We found no significant effect of anti-coagulant and anti-aggregation drug use on catheter thrombosis.

In patients with low albumin is related coagulation tendency. Folsom et al. reported that low serum albumin levels reflect the state of hypercoagulability, and low serum total protein levels are not always associated with this situation (22). Despite the fact that the study included a small group, albumin and total protein levels were not as low as in the nephrotic syndrome. In our study, we found a correlation between the levels of baseline albumin and total protein. In the thrombotic group, ferritin levels were significantly increased. Although increased CRP levels were statistically insignificant, they may have had some clinical importance. An increased level of ferritin and CRP seems to emerge as an acute phase reactant associated with thrombosis.

Future studies should be aimed at evaluating the use of thrombolytic therapy as the prophylaxis of catheter thrombosis.

Ethics Committee Approval: The research was conducted with the approval number 2013-27-26/02 of Bülent Ecevit University Ethics Committee. Authors declared that this research was conducted according to the principles of the World Medical Association Declaration of Helsinki “Ethical Principles for Medical Research Involving Human Subjects”, (amended in October 2013).

Informed Consent: Informed consent is not necessary due to the retrospective nature of this study.

Peer-review: Externallypeer-reviewed.

Author Contributions: Concept - K.M.; Design - K.M.; Supervision - K.M., E.H.; Resources - K.M.,E.H., B.T., İ.Y.; Materials - K.M., B.T., C.Ç., N.Y.; Data Collection and/orProcessing - K.M., B.T.,C.Ç., N.Y., E.H.; Analysis and/

orInterpretation - K.M., F.K., E.H.; Literature Search - K.M.,E.H.; Writing Manuscript - K.M.; Critical Review - K.M., E.H., İ.Y., G.Y.; Other - G.Y.

Conflict of Interest: The authors have no conflicts of interest todeclare.

Financial Disclosure: The authors declared that this study has received no financial support.

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