Original Article

ARTERIOVENOUS FISTULA THROMBOSIS IN PATIENTS ON REGULAR HEMODIALYSIS: A REPORT OF 171 PATIENTS

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Background: Fistula thrombosis in patients on maintenance hemodialysis is an important morbidity factor. Arterial or venous thrombotic events have been described as complications in patients on regular hemodialysis. This study was designed to evaluate the risk factors for arteriovenous fistula thrombosis.

Methods: One hundred and seventy-one patients with arteriovenous fistula on maintenance hemodialysis were studied prospectively during a period of 14 months for any episode of arteriovenous fistula thrombosis, after anticardiolipin antibodies were assayed by ELISA. Other risk factors for thrombosis such as the presence of diabetes or hypertension, the use of erythropoietin (rhEPO), fistula site, gender, age, ultrafiltration, hypotension during dialysis, and the number of dialysis visits in a week were assessed.

Results: Fifty-six percent of patients had IgG-anticardiolipin antibodies ≥ 10GPL, which was significantly correlated with dialysis duration (23.18 ± 24.56 months in patients with anticardiolipin antibodies ≤ 10GPL vs. 37.73 ± 36.35 months in patients with 20 ≤ IgG-anticardiolipin antibodies < 40GPL). Within the 14 months of follow-up, 36 episodes of arteriovenous fistula thrombosis occurred in 31 patients (18.1%). Considering anticardiolipin antibodies and other risk factors in a Cox proportional hazard model, only fistula site (P = 0.021, RR = 2.48, CI = 1.14 – 5.37) and erythropoietin (Eprex) use (P = 0.021, RR = 10.92, CI = 1.43 – 83.02) seemed to have an influence on fistula patency. According to fistula site, the survival of brachiocephalic fistulas were significantly (P = 0.007) better than radiocephalic ones (1- and 3-year survival were 95% and 87% for upper, and 88% and 72% for lower ones, respectively).

Conclusion: Although the incidence of the anticardiolipin antibody was high in our patients, in the presence of other risk factors for thrombosis, we found no correlation between IgG-anticardiolipin antibodies and arteriovenous fistula thrombosis. Instead, erythropoietin (Eprex) use and fistula site seem to have an important role in the correlation between IgG-anticardiolipin antibodies and arteriovenous fistula thrombosis.

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Keywords: Anticardiolipin antibody (ACLA) • Eprex • fistula • fistula thrombosis

Introduction

Thrombosis of arteriovenous communications used for chronic hemodialysis remains a major cause of morbidity in hemodialysis patients. In addition to significant morbidity, it has been estimated that about 500 $ million is spent each year in the United States to create and maintain vascular access.[1] A recent report of the US Renal Data System (USRDS) found an overall primary access patency rate of only 53% at one year.[2] Intimal fibromuscular hyperplasia at the venous anastomosis may be an important factor associated with thrombosis.[3] Some other factors include: the presence of diabetes,[4] the location of the graft,[5] age of more than 65 years,[2] hypoalbuminemia,[6] elevated lipoprotein,[7] hyperhomocycteinemia,[8] and presence of anticardiolipin antibodies (ACLAs). The only definite risk factor for vascular access thrombosis is the placement of a synthetic graft rather than a native arteriovenous fistula (AVF).

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Anticardiolipin antibody (IgG-ACLA) is strongly associated with venous and arterial thrombosis in patients with normal renal function.[9] Also, it has been suggested as a risk factor for renal allograft failure.[10] The reported prevalence of elevated ACLA titers in dialysis patients varies widely in different studies from 0.7% – 69%.[11] The mechanism of production of ACLA is still in doubt. While the relation between antiphospholipids and hypergammaglobulinemia[12] or anti-DNA antibody[13] was described previously, new observations suggest that the production of ACLA may be a reaction to the membranes to which the patients are exposed during hemodialysis.[14 – 16] The objective of the present study was to evaluate the risk factors for AVF thrombosis, (AVFT) in patients on regular dialysis.

Patients and Methods

In this cohort study, 187 patients with end-stage renal disease (ESRD) undergoing chronic hemodialysis treatment in three centers in university-based teaching hospitals in Shiraz, Iran were analyzed. None of the selected patients had acute infection based on physical signs and laboratory data. Patients underwent conventional low-flux hemodialysis, using either a cuprophan or polysulofan hollow fibers dialyser without reusing, performed against a sodium acetate dialysate bath. The average length of each dialysis was 3 ½ hours. Whenever thrombosis of an AVF occurred, a subclavian catheter was inserted and a new fistula was created at another site.

After explaining the aims of the study and obtaining informed consent from each person included in the study, 10 mL of blood was obtained from the arterial line prior to the circulation of blood through the dialyser and was placed into glass tubes without the use of a syringe, using only arterial blood flow. Samples were centrifuged at 3000 rpm for 15 min, within 1 ½ hours of sampling, at room temperature. For ACLA, the supernatant serum was quickly frozen and stored at –20°C.

In all patients, age, duration of dialysis, and number of dialysis sessions in a week were assessed from their medical records. Prior history of AVFT, which was defined as the failure of patency after the first 30 days of placement was obtained through direct questioning. Only thrombotic events with complete vascular occlusion were reported.

All selected patients, at the beginning of the study, were evaluated before each session for any signs of obstruction (absence of auscultatory sound or palpable thrill) and if present, Doppler ultrasonography was done as soon as possible to confirm complete obstruction by clotting.

In each session, hypotension episodes and number of injections in each fistula were recorded on special forms. After the end of the study, those forms were analyzed as follows: if hypotension occurred in more than 50% of all sessions, it was considered as "hypotension during dialysis". According to our hypothesis, the number of fistula injections, a minor trauma to the vessel's intima, can be a risk factor for AVFT. However, in our study centers, we did not see a significant increase in the injection number (more than two times) due to the personnel's experience. During the 14 months of follow-up, 42 patients (24.6%) expired and 36 (21.1%) were transplanted. Other fistula complications such as aneurysms or traumatic obstructions were excluded. Patients receiving methyldopa, hydralazine, or sodium valproate and those receiving aspirin for previous CVA or CHD were identified.

Exclusion criteria: patients were excluded if they were diagnosed with SLE; if they had acute infection; or if they had any neoplastic disorders (all of these clinical conditions were previously related to the presence of ACLA).

Laboratory procedures

For ACLA, wells of ELISA plates were coated with cardiolipin in ethanol, and the ethanol evaporated at 4ºC overnight. Spectrophotometric evaluation indicated the presence or absence of ACLA. Results were obtained by reading the absorbance at 490 nm and values were reported as IgG phospholipid (GPL) units. Values were considered negative when ACLA < 10 GPL, low positive when 10 ≤ ACLA < 20 GPL, medium positive when 20 ≤ ACLA < 40 GPL, and highly positive when ACLA ≥ 40 GPL units.

Statistical analysis

Data are expressed as mean ± SD for continuous variables. Patients with positive and negative titers of ACLA were analyzed demographically. Factors suspected of being associated with thrombosis were compared between the two groups—those with and without

thrombosis—using the Pearson's Chi-square test. The *t*-test was done for continuous variables as appropriate. The fistula survival was analyzed by Kaplan-Meier method. Covariates for fistula survival were analyzed using the Cox proportional hazard model. In this model, all nominal data were coded as either present or absent. Fistula patency was calculated since the insertion of fistula (in all cases prior to the beginning of the study) until the time of death, transplantation, or if no events had occurred, in September 2002. All *P* values reported are 2-sided and *P* values < 0.05 were considered statistically significant.

Results

Of 187 patients, 8 patients were excluded due to SLE, four with acute infection, and four due to malignancy at the onset of the study. There were 116 males (67.8%) and 55 females (32.2%). All patients had either side-to-side brachiocephalic (n = 98) or radiocephalic (n = 73) AVFs that were patent at the beginning of the study, with palpation and auscultation. Diabetes (26.9%) was the most common cause of ESRD in our population. The majority of our patients (73.4%) were given subcutaneous erythropoietin [EPO; Eprex (Epoetinα)] in syringes containing 2000 IU/ 0.5 mL once, twice, or 3 times weekly. Of those receiving EPO, 95% were on maintenance treatment. The mean ± SD for age and dialysis duration were 53.08 ± 15.3 years and 25.24 ± 21.04 months, respectively, in our patients. Fistula follow-up time was 23.01 ± 21.53 months (range: 1 – 144 months). Sixteen patients (9.4%) had previous AVFT. Seven of these (43%) experienced another AVFT during the follow-up period, which was significant in comparison to patients with no history of previous AVFT (43% vs. 15%, $P < 0.05$).

Fistula thrombosis

Thirty-six episodes of AVFT, documented with Doppler ultrasonography, occurred in 31 patients (18.1%). Five patients experienced recurrent AVFT (more than 2 times) within our 14 months of follow-up period; 3 with low positive and 2 with IgG-ACLA < 10 GPL. Among patients who experienced AVFT during the study, 22.6% had a previous history of AVFT (7 out of 31), which was significantly higher than those who had not experienced previous thrombosis (9 out of 140) ($P = 0.005$). We found an increasing incidence of thrombosis among patients receiving Eprex 0, 1, 2, or 3 times weekly (4.5% to 14.3 % to 27.3% to 27.3%, respectively). There was a significant difference in thrombosis between patients not receiving Eprex (3 out of 45) and those receiving it one, 2, or 3 times weekly (28 out of 126) ($P = 0.02$). Of the 171 AVFs, in lower fistulas, thrombosis occurred in 20 out of 73 and in upper ones, 11 out of 98 (27.4% vs. 11.2%, $P = 0.007$). Thrombosis among patients older than 45 (28 out of 127) years was significantly higher than patients younger than 45 (3 out of 44) (22% vs. 6.8%, $P = 0.016$). Eleven out of 36 patients dialyzed with more than 3 liters ultrafiltration, experienced thrombosis. It was significantly more than those dialyzed with less than 3 liters ultrafiltration (20 out of 134, $P = 0.031$) (Table 1).

In order to define the influence of fistula site on the AVF survival, we used the Kaplan-Meier method (Figure 1). Patients who left the dialysis system, through death or transplant, were censored for this procedure. In this analysis, patients with upper AVF experienced longer survival than those with lower AVF ($P = 0.007$). Even if patients with

Table 1. Access thrombosis during the study in 171 patients.

	AVFT (+)	AVFT (–)	*P* value
Gender			
Male	19	97	0.38
Female	12	43	
Age (years)			
<45	3	41	
≥45	288	99	
Cause of ESRD			
Diabetes and hypertension	16	68	0.75
Others	15	72	
Fistula site			
Brachiocephalic	11	87	0.007
Radiocephalic	20	53	
Previous AVFT			
Yes	7	9	0.005
No	24	131	
Eprex injection			
Yes	28	98	
No	3	42	
ACLA			
Positive	16	81	0.52
Negative	15	59	
Hypotension during dialysis			
Yes	16	59	0.33
No	15	81	
Ultrafiltration			
≥3 liters	11	25	0.029
<3 liters	20	115	

a previous history of AVFT were excluded, this significance persisted (P = 0.0144). Survival was not significantly different among patients with diabetes and hypertension, and did not significantly differ by gender. To determine the role of fistula site on fistula patency in the presence of other covariates, we analyzed the data using a Cox proportional hazard model (Table 2). As listed in Table 2, the only factors that significantly influenced fistula patency, were fistula site (P = 0.021, RR = 2.48, CI = 1.14 - 5.37) and Eprex use (P = 0.021, RR = 10.92, CI = 1.43 – 83.02).

Table 2. Analysis of covariates by Cox proportional multivariate analysis.

Covariates	RR	95% CI	*P* value
Age	1.03	1.000; 1.062	0.050
Sex (female)	1.65	0.695; 3.942	0.255
Diabetes (present)	1.28	0526; 3.131	0.583
Hypertension (present)	2.065	0.861; 4.952	0.104
Number of dialysis episodes during one week (three)			
One	1.817	0.460; 7.179	0.394
Two	1.402	0.523; 3.757	0.501
Fistula site (upper)	2.48	1.145; 5.370	0.021
Eprex use	10.92	1.437; 83.027	0.021
Positive ACLA	2.154	0.941; 4.930	0.069
Ultrafiltration≥3L	1.775	0.794; 3.971	0.162
Hypotension during dialysis	1.106	0.509; 2.406	0.799

RR = relative risk.

ACLA titers and correlations

Seventy-four patients (43.3%) had an IgG-ACLA less than 10 GPL, 85 (49.7%) had an IgG-ACLA between 10 to 20 GPL, 11 (6.4%) had an IgG-ACLA between 20 to 40 GPL, and only one patient had an IgG-ACLA that was equal to 40 GPL. ACLA values were considered positive when they were greater than or equal to 10 GPL. Patients older than 55 years tended to have positive titers of ACLA more than patients younger than 55 years (61% vs. 51%); although, this was not statistically significant. Patients with low and medium positive titers of IgG-ACLA had been on dialysis longer and had a great number of dialysis sessions (dialysis duration × 4 × times of dialysis in a week) in comparison with patients with negative values (222.92 vs. 391.9 vs. 201.86, respectively, P = 0.057 for low and medium, and $P < 0.05$ between negative and medium titers). Presence of ACLA was not more frequent in patients receiving methyldopa, hydralazine, or sodium valproate in comparison to those not receiving those drugs (38% vs. 58%). Instead, 10 out of 12 (83%) of patients using aspirin due to previous CVA or CHD had positive titers of IgG-ACLA. Among them, only one patient experienced AVFT.

Discussion

In recent years, there have been an increasing number of reports of ACLA in patients with non-SLE disorders.[17 – 19] For the first time, Gronhagen-

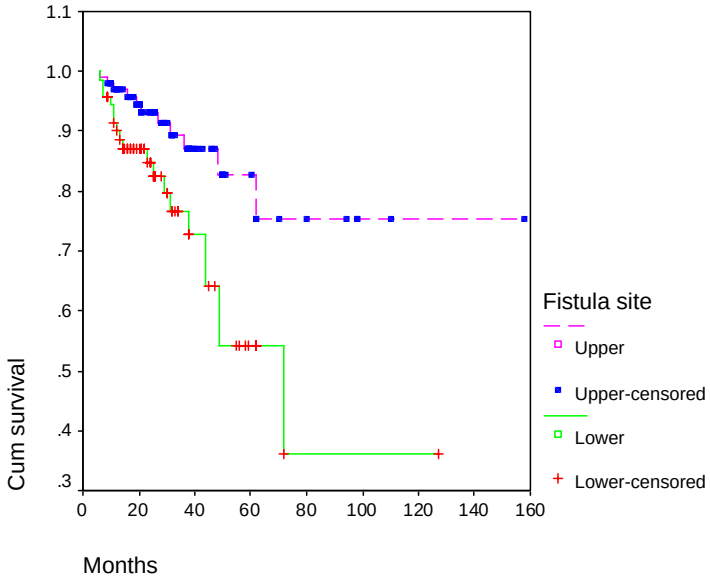

Figure 1. Kaplan-Meier method of analysis of thrombosis according to fistula site ("months" indicate duration of fistula since insertion till the end of study or thrombosis, in patients with AVFT).

Riska et al [20] reported the presence of ACLA in a hemodialysis population. Previously, it was reported that drug-related antibodies are predominantly IgM-ACLA rather than IgG class.[21] The prevalence of positive titers of ACLA in our population is high in comparison to other studies, as we considered it positive in patients with IgG-ACLA ≥ 10 GPL, while others have previously assumed it positive when it was more than 15 GPL or even 23 GPL. It has been speculated that ACLA arises as a response to foreign antigens present in bacteria,[24] such as endotoxins that contain phosphate groups with similar distribution to cardiolipin. The correlation between ACLA titer and length of dialysis can be explained by the fact that these patients are regularly exposed to endotoxins present in the dialysate. Shorter periods of dialysis in our patients (24.2 ± 22.4 months) can explain the higher incidence of low titers of ACLA in comparison with higher titers in other published series (which reported 37 – 52 months of dialysis). Some studies believe that uremia is a form of an immunodeficiency state in which autoimmunity may develop due to altered immune function.[25, 15] They think that dialysis, because of the contact of blood with bioincompatible surfaces such as the dialyser, can exacerbate this autoimmunity.[23] Although in patients with SLE, the presence of ACLA has been associated with vascular thrombosis, the role of ACLA in thrombosis of vascular access in hemodialysis patients is still controversial. Our study was a large prospective one that showed no association between IgG-ACLA and AVFT. Also, Fabrizi et al,[26] Chew et al,[22] Prakash et al,[16] Valeri et al,[11] and others[14, 15, 19] have found no significant association between high titers of IgG-ACLA and AVFT, while others[20, 27] did find such an association.

Like Dixon et al,[28] our patients with radiocephalic (lower) fistulas had significantly more thromboses than patients with brachiocephalic (upper) fistulas ($P = 0.014$). Survival rates for fistula in the present study are better than those reported in recent studies. For upper AVF, cumulative 1- and 3-year patency rates have been reported to be between 67% to 84% and 50% to 78%, respectively.[29 – 32] For lower AVF, recent studies report 1- and 3-year patency rates of 48% to 69% and 36% to 48%, respectively.[33, 34, 37, 38] In our study, 1- and 3-year patency was 95% and 87% for upper and 88% and 72% for lower fistulas. Some other studies showed that upper fistulas can improve short-term outcomes in women, older patients, and those with diabetes for whom establishment of a lower fistula is difficult.[35, 36] In our population, AVFT increases steeply with age (more than 45 years), a fact that has been confirmed by others.[2, 37] It is possible that the vessel's anatomy or other patient characteristics that were not recorded, influenced access thrombosis, a fact that can be confirmed by a significant relation between previous AVFT and new ones during the follow-up period ($P < 0.05$). The role of the surgeon in fistula patency also has been mentioned by Prischl et al[38] and Dixon et al,[28] who showed it as a major factor in both short-term and long-term patency of radiocephalic fistulas. Most of our fistulas were created by various surgeons in different hospitals. So, we were unable to study the role of the surgeon in AVFT. Also, our study may not have had sufficient power to confirm some of the previously described risk factors such as decreased access flow as a predictor of thrombosis.

Another theory for the occurrence of thrombosis in hemodialysis patients is homeostatic problems that may predispose them to hypercoagulability. There are some studies focusing on elevated factor VIII coagulant activity,[39] decreased release of plasminogen activator in response to venous occlusion,[40] reduced platelet sensitivity to antiaggregatory prostacyclines,[41] or reduced antithrombin III, protein S, and plasminogen.[42] Regarding the role of EPO, studies are equivocal as to whether recombinant human erythropoietin (rhEPO) increases thrombosis in fistulas or not. Taylor et al[43, 44] showed increased thrombin antithrombin III complex, collagen, and ADP aggregation in patients using EPO even when EPO was withdrawn. We also found an increasing incidence of thrombosis in EPO injectors (22% vs. 4.5% in those not using EPO, $P = 0.02$). On the contrary, Churchill et al[45] believe that EPO does not increase the probability of fistula thrombosis. The latest discussion on the relation of EPO with thrombosis was by Ikegaya et al[46] who think that thrombosis occurs at stenotic segments of fistula where they showed significant enhancement of erythropoietin receptors and transforming growth factor-β (TGF-B).

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