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The role of antiplatelet therapy on arteriovenous fistula malfunctioning among hemodialysis patients

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Abstract

Background and objectives: The vascular access of choice for hemodialysis is the Arteriovenous fistula. A functional vascular access is required for a successful hemodialysis performance. The aim of the study is to examine the effect of antiplatelet therapy on arteriovenous fistula malfunctioning among hemodialysis patients.

Methods: A cross-sectional study on 78 end-stage renal disease patients who undergone hemodialysis and had arteriovenous fistula was conducted. The data were collected during the period of 1st April 2020 to 1st April 2021, taking information about socio-demographic data of the patients such as age, gender, past medical history and hemodialysis status.

Results: The mean age of patients was 63.87 (± 8.44) years; most of them were female and smokers. Only 17.9% of the patients were not on erythropoietin, while the rest were taking 8000 IU/week (55.1%) or 4000 IU/week (26.9%). After one year of having arteriovenous fistula, more than half (52.6%) of the patients developed arteriovenous fistula malfunctioning in the form of stenosis (17.95%) or thrombosis (34.62%). There were significant statistical associations between arteriovenous fistula malfunctioning and comorbidities, type of anti-platelet and use of erythropoietin. However, non-significant statistical association was found between the development of arteriovenous fistula malfunctioning and gender, duration of hemodialysis and smoking.

Conclusions: Antiplatelet therapy and lower doses of erythropoietin use is associated with lower arteriovenous fistula malfunctioning. Prior to the arteriovenous fistula creation, patients should be assessed appropriately.

Key words: Antiplatelet therapy; Arteriovenous fistula; Hemodialysis; Malfunctioning.

Introduction

The rates of mortality and morbidity in end-stage renal disease (ESRD) patients are high. To maintain a high quality of life in the ESRD patients, adequate dialysis is necessary. Vascular access is also recognized as a “lifeline” for patients receiving hemodialysis.[1] Accessing the blood vessels that are efficient in providing rapid extracorporeal blood flow is what hemodialysis requires.[2] This requirement is best achieved by arteriovenous access. This can be achieved by arteriovenous fistulas (AVF), arteriovenous grafts (AVG) and central vein catheters.[1-2] The vascular access of choice for hemodialysis is the AVF.[3] The anatomy of the fistula varies depending on its site in the body. For hemodialysis, AVFs are usually formed in the extremities, with the upper limbs being commonly favoured over the lower limbs by vascular surgeons. The cephalic and basilic veins and the radial and the brachial arteries are often used for the creation of hemodialysis. The radio-cephalic AVF is considered the desired primary vascular access for hemodialysis.[4-5] A functional vascular access is required for a successful

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hemodialysis performance. A native fistula is the ideal type of access as the risk of complications and need for interventions are at lowest, and it also provides a long-term patency.[6] Nevertheless, a major obstacle in the long-term success of hemodialysis therapy is AVF dysfunction.[5] In AVF creation, the best method to decrease the risk of primary AVF failure involves introducing hemodialysis vascular access early, performing vascular mapping, and assessing newly created AVFs at four weeks.[7] The rate of blood flow of vascular access and its patency are directly linked with adequacy of the dialysis. Frequent hospitalizations and requiring intervention are complications connected with vascular access. Such complications have substantial impacts on the morbidity and mortality of hemodialysis patients, as well as contributing to excessive medical costs. Therefore, maintaining a well-functioning vascular access is essential.[1,8] However, it is challenging to preserve a functioning vascular access for hemodialysis patients.[9] One of the important causes of morbidity in the hemodialysis patients is a vascular access dysfunction. Inadequate maturation of the vein and early thrombosis (within the first several weeks following surgical creation) are the primary causes of native fistula failures. Therefore, early fistula evaluation (4–6 weeks after its creation) is considered important. Failure to adequately develop recurring cannulation for dialysis, insufficient flow to maintain the dialysis, and thrombosis formation are the most common clinical manifestations of early fistula failure. Juxta-anastomotic stenosis is the typical pathology that leads to AVF failure. Numerous studies have indicated that the AVF failure frequency can be reduced with taking antiplatelet agents.[6,10] The leading cause of vascular access failure is thrombosis, which commonly occurs due to stenotic lesions in the intravenous outflow system.[1,8] Antiplatelet agents and anticoagulants have been used to prevent vascular access thrombosis, as it is one of the most common complications of hemodialysis shunts. Furthermore, over the past few decades, different medications such as antiplatelet agents and warfarin have been studied for the vascular access thrombosis prevention. The most established advantage of antiplatelet agents was vascular access patency.[1] For hemodialysis patients, clopidogrel appears to be safe and effective for prevention of primary AVF failure.[6] To our best knowledge, there have been no studies in Erbil/Iraq to examine the AVF malfunctioning among hemodialysis patients and its association with the antiplatelet therapy. Therefore, this study aimed to examine the effect of antiplatelet therapy on AVF malfunctioning among hemodialysis patients with chronic disease.

Patients and methods

A cross-sectional study was adopted in this study. The data collected from the patients who admitted to Erbil Dialysis Unit, Erbil Teaching Hospital, Erbil city/Iraq.The sample of the current study comprised of 78 ESRD patients who undergone hemodialysis and had AVF. The data were collected during the period of 1st April 2020 to 1st April 2021. After extensive review of literature, a questionnaire was designed and used to collect data from patients who undergone hemodialysis. The questionnaire composed of two main parts including the socio-demographic data of the patients such as age, gender, past medical history…etc. The second part of the collected data comprised information about hemodialysis, types of AVF, AVF malfunctioning, and use of anti-platelet therapy. The data were analyzed using the Statistical Package for Social Sciences (IBM SPSS Statistics, IBM Company, USA; version 25) and according to the variables, descriptive and inferential statistics were applied with a statistical significance level of ≤ 0.05. The results

presented as frequencies, percentages in tables and figures and analyzed using Chi square tests or Fisher's exact tests if necessary.Ethical approval was obtained from the Research Ethics Committee at Kurdistan Higher Council of Medical Specialties. The confidentiality and anonymity of patients were safeguarded. Verbal consent was obtained from the patients prior to their participation in the study.

Results

In the current study a total of 78 hemodialysis patients were included, with mean age of 63.87 ± 8.44 years. The youngest participant was 39 years old while the eldest was 75 years old. Most of the participants were female (52.6%) and smokers (60.3%). The entire study sample had some sort of chronic diseases including diabetes or dyslipidemia as the primary comorbidity in addition to other conditions. The duration of hemodialysis was varying considerably among the patients with 8 hours/week as the most frequent occurring followed by 9 hours/week. Only 17.9% of the patients were not on erythropoietin, while the rest were taking 8000 IU/week (55.1%) or 4000 IU/week (26.9%). For most of the patients (61.5%), no any sort of anti-platelet was prescribed by the nephrologist, however, aspirin was prescribed for 26.9% of them. Brachiocephalic was the commonest type of AVF (82.1%). After one year of having AVF, more than half (52.6%) of the patients developed AVF malfunctioning in the form of stenosis (17.95%) or thrombosis (34.62%) (See Table 1 and Figure 1).

Table (1): Background data of the study sample

Variables	**Categories**	**No.**	**%**
Gender	male	37	47.4
	female	41	52.6
Smoking	yes	47	60.3
	no	31	39.7
Comorbidities	DM	3	3.8
	Dyslipidemia	1	1.3
	DM, IHD & dyslipidemia	20	25.6
	DM & dyslipidemia	42	53.8
	DM, HTN, IHD, dyslipidemia	12	15.4
Duration of hemodialysis	6 hours/week	10	12.8
	7 hours/week	2	2.6
	8 hours/week	41	52.6
	9 hours/week	25	32.1
Use of erythropoietin	no	14	17.9
	8000 IU/week	43	55.1
	4000 IU/week	21	26.9
Type of anti-platelet	no	48	61.5
	aspirin	21	26.9
	aspirin & Clopidogril	7	9.0
	aspirin & ticagrelor	2	2.6

Type of AVF	radiocephalic	14	17.9
	brachiocephalic	64	82.1
AVF malfunctioning	no	37	47.4
	yes	41	52.6
	Total	78	100

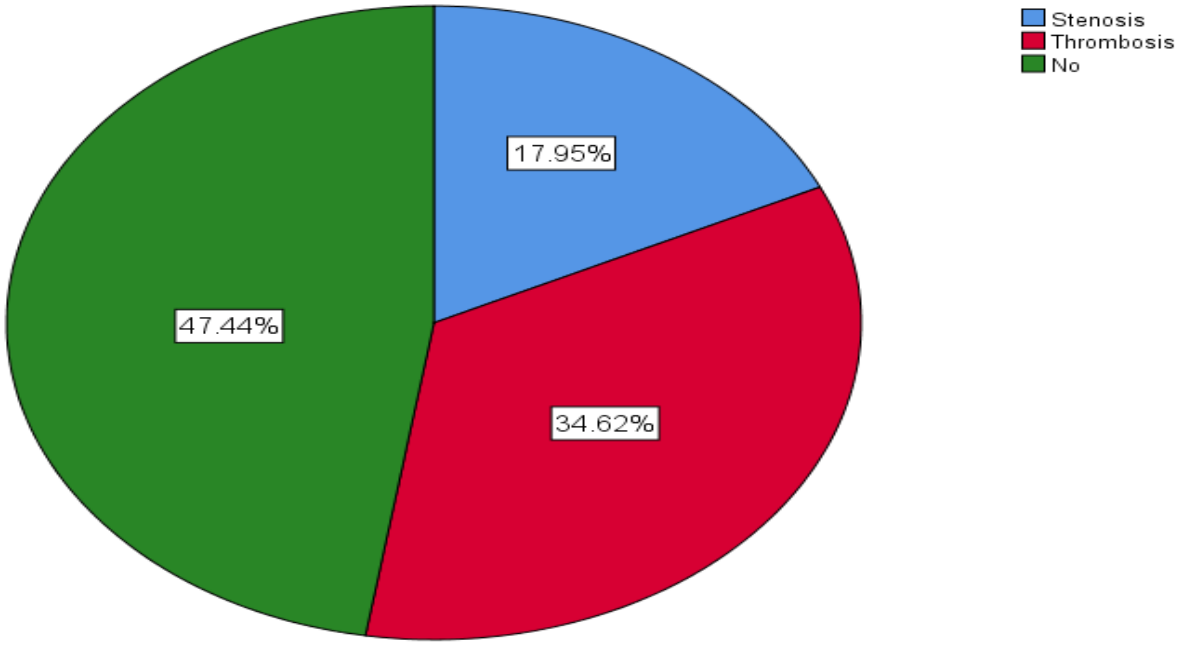

Figure (1): Types of AVF mal-functioning among hemodialysis cases.

The results of Table (2) show that there was a significant statistical association between AVF malfunctioning and comorbidities, type of anti-platelet and use of erythropoietin. All the patients with diabetes alone, and (83.3%) of patients with diabetes mellitus (DM), hypertension (HTN), ischemic heart disease (IHD) and dyslipidemia developed AVF malfunctioning while the patients with other comorbidities experienced less AVF malfunctioning. Pearson Chi square test was applied and p–value was 0.026. Regarding the use of anti-platelets, patients who were taking dual therapy of aspirin and ticagrelor; did not develop AVF malfunctioning in the same way as the majority (71.4%) of those who were taking aspirin alone. In contrary, the majority of patients without anti-platelet therapy (62.5%) or those were on a combination of aspirin and clopidogril (71.4%) finally developed AFV malfunctioning (p= 0.014). The association between the use of erythropoietin and AFV malfunctioning was remarkable in such a way that all those who did not use it, or majority (62.8%) of those who were put on 8000 IU/week regimen experienced the malfunctioning, in contrast, none of the patients on 4000 IU/week regimen had developed any malfunctioning, Pearson Chi square test was carried out and p-value was 0.001.

Table (2): Association between AVF mal-functioning and comorbidities, type of anti-platelet and use of erythropoietin.

Variable	Categories	AVF malfunctioning		p-value
		no	yes	
Comorbidities	DM	0 (0%)	3 (100%)	0.026
	Dyslipidemia	1 (100%)	0 (0%)	
	DM, IHD, dyslipidemia	12 (60%)	8 (40%)	
	DM, dyslipidemia	22 (52.4%)	20 (47.6%)	
	DM, HTN, IHD, dyslipidemia	2 (16.7%)	10 (83.3%)	
Type of anti-platelet	no	18 (37.5%)	30 (62.5%)	0.014
	aspirin	15 (71.4%)	6 (28.6%)	
	aspirin, clopidogril	2 (28.6%)	5 (71.4%)	
	aspirin, ticagrelor	2 (100%)	0 (0%)	
Use of erythropoietin	no	0 (0%)	14 (100%)	0.001
	8000 IU/week	16 (37.2%)	27 (62.8%)	
	4000 IU/week	21 (100%)	0 (0%)	

The results of Table 3 show that there was non-significant statistical association between the development of AVF malfunctioning and gender, duration of hemodialysis, smoking and type of AVF. Chi square test was done and p–values in all conditions were more than 0.05.

Table (3): Association between AVF malfunctioning and gender, duration of hemodialysis, smoking and type of AVF.

Variable	Categories	AVF malfunctioning		p-value
		no	yes	
Gender	male	17 (45.9%)	20 (54.1%)	0.802
	female	20 (48.8%)	21 (51.2%)	
Duration of hemodialysis	6 hours/week	6 (60%)	4 (40%)	0.792
	7 hours/week	1 (50%)	1 (50%)	
	8 hours/week	20 (48.8%)	21 (51.2%)	
	9 hours/week	10 (40%)	15 (60%)	
Smoking	yes	23 (48.9%)	24 (51.1%)	0.744
	no	14 (45.2%)	17 (54.8%)	
Type of AVF	radiocephalic	6 (42.9%)	8 (57.1%)	0.705
	brachiocephalic	31 (48.4%)	33 (51.6%)	

Discussion

This study examined the effect of antiplatelet therapy on AVF malfunctioning among hemodialysis patients with chronic disease. The analysis indicated that more than half of the study sample developed AVF malfunctioning after one year of having AVF. The most common types of malfunctioning were

stenosis and thrombosis. The effectiveness of dialysis is determined by the AVF patency, which is considered the primary determinant of dialysis effectiveness. Epidemiological, clinical, biological, pharmacological, and anatomical are the main determinants of the AVF patency .[3] Fistula evaluation 4 to 6 weeks after its creation is deemed necessary.[10] Our analysis revealed that the whole study sample had some kind of chronic diseases such as diabetes mellitus, dyslipidemia, ischemic heart disease, and hypertension. Likewise, Zouaghi reported that 80% of their sample, besides to chronic kidney disease, had at least one chronic disease.[3] One of the risk factors of AVF malfunctioning in HD patients was hyperinsulinemia; this could explain the added risk of loss of the AVF patency in diabetic patients.[8]The current study findings revealed that there was a statistically significant association between comorbidities and AVF malfunctioning. Similarly, Zouaghi[3] concluded that in the elderly, comorbidities including diabetes mellitus, ischemic cardiomyopathy, and atherosclerosis increase the risk of primary AVF failure and impair its patency. Although our analysis indicated that diabetes was associated with AVF malfunctioning, Zouagh[3] reported that in their patients, diabetes was not a contributing factor in the patency of AVF. The current study analysis indicated that gender was not associated with AVF malfunctioning. In contrary, Wen found out that females had a higher incidence of AVF failure (p= 0.025).[5] The use of erythropoietin was significantly associated with AVF malfunctioning (all those who did not use it and those with higher doses). However, taking cautious decision by clinicians regarding the effective dosage prescription of erythropoietin for their patients is quite essential, due to the fact that our analysis suggests that those patients who were put on higher doses (i.e., 8000 IU/week) of erythropoietin experienced the AFV malfunctioning. A recent study recommends prescribing lower doses of erythropoietin for those patients at risk of AVF stenosis, as they found that the median of weekly doses of erythropoiesis-stimulating agent was higher in cases (8000 IU) than in controls (5000 IU).[11] Wärme also concludes that high doses of erythropoietin are associated with AVF complications.[12] Another study also reported that in patients with AVF failure, the average weekly dose of erythropoietin stimulating agents was significantly higher (4782.2 IU/mL/week vs. 7161.8 IU/mL/week) and they suggested that erythropoietin stimulating agents may contribute to late AVF failure.[13] The U.S. Food and Drug Administration (FDA) recommended "more conservative dosing" of erythropoiesis-stimulating agents in patients with chronic kidney disease to improve the safe use of such medications. It recommended that the therapy should be individualized and the lowest possible dose of erythropoietin stimulating agents should be given to reduce the need for transfusions.[14] Nevertheless, the issue of the safe dose of erythropoietin should be further investigated.Our study identified that the patients who used antiplatelets (aspirin alone and dual therapy of aspirin and ticagrelor) did not develop AVF malfunctioning. Similarly, Palmer conducted a meta-analysis and systematic review of 21 randomized controlled trials on adults (4,826 participants) on long-term hemodialysis therapy.[15] They compared antiplatelet therapy with placebo or no antiplatelet therapy. It was found that antiplatelet therapy decreased fistula malfunctioning including thrombosis or loss of patency by one-half.[15] In addition, Coleman reported that antiplatelet agents reduce the rate of AVF thrombosis.[16] However, the antiplatelet therapy had unclear effects on major bleeding.[15]Mousa documented that aspirin alone is not less effective to aspirin and clopidogrel.[9] Li conducted a retrospective study on 121 patients to investigate the factors

associated with primary dysfunction of AVF and it was found that patients with fistula dysfunction had hyperlipidemia.[17] In addition, De Marchi reported that hyperinsulinemia is linked with AVF thrombosis. Therefore, assessing these factors could be useful in identifying patients at risk of fistula stenosis and thrombosis.[8] Furthermore, Locham conducted a study to assess the role of antiplatelet therapy in patients with hemodialysis undergoing AVF. It was found that the risk of in-hospital mortality was a 12-fold increase in patients on no-antiplatelet therapy vs. antiplatelet therapy.[18] This means that antiplatelet therapy was linked with lower in-hospital mortality. Use of antiplatelet therapy (aspirin and P2Y12-inhibitors) among AVG patients demonstrated improved primary patency rates. Locham recommended the use of antiplatelet therapy especially in patients on AVG.[18] Additionally, Zouaghi reported that non-use of antiplatelet medications considerably impaired the secondary patency.[3]

Limitation

In the current study, a small sample size could be considered as a limitation of this study. Therefore, further study involving a larger sample size is needed in future.

Conclusions

Antiplatelet therapy and lower doses of erythropoietin use is associated with lower AVF malfunctioning. Prior to the AVF creation, patients should be assessed appropriately. It is recommended that fistula evaluation in early weeks after its creation is deemed essential.

Conflicts of interest

The author reports no conflicts of interest.

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