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Original Article

Association between Raised Serum C-Reactive Protein and Arteriovenous Fistula Failure

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Abstract

Objectives: To study the association between serum C-reactive protein (CRP) and arteriovenous fistula (AVF) failure rate.

Patients and Methods: This case control study Department of Vascular Surgery Combined Military Hospital Lahore and Peshawar between January 2015 and March 2016. Total 126 consecutive patients who had serum CRP checked preoperatively and underwent AVF procedure were included. Patients were divided into Case (with raised CRP) and Control (Normal CRP) groups. Data regarding serum CRP level were recorded and analysed to evaluate the impact of preoperative CRP levels on AVF failure rates.

Results: The AVF failure rate was significantly high (53.2%) in case group as compared to control group (14.5%). Age, gender, diabetes and hypertension did not show statistically significant difference between the two groups.

Conclusion: Raised level of CRP is related to significantly higher AVF maturation failure rate. Therefore, it is recommended to check CRP levels preoperatively to identify those patients who can be at higher risk of fistula failure.

Keywords: Arteriovenous fistula, Association, C-reactive protein

Introduction

The morbidity and mortality in end stage renal disease (ESRD) patients has been decreased with recent advances in medicine and improvement in general health measures in spite of increased prevalence of the disease.[1,2] The major role in improving the survival of ESRD patients has been played by hemodialysis (HD) as renal replacement therapy.[3] HD needs vascular access and the best way of getting this vascular access is by creating an AVF.[4] AVF can be a good option due to decrease rate of complication and increase durability. But increase tendency of vasospasm in small vessels decreases its effectiveness and can lead to both early and late failures. In a clinical setting, early failure of AV fistula can be defined as fistula that does not have any effective development for dialysis or after initiation of dialysis failure occurs within 3 months. Late failure is defined as malfunction after successful use. Definition of adequate AV fistula based on rate of blood flow, diameter of fistula and its distance from skin. Early failure or failure to maturity is main issue in about 23% to 46 % of all AV fistulas.

AVF has to be functionally mature before its use. Many factors like advancing age, female gender, smoking, diabetes, hypertension, hyperlipidemia, hyperparathyroidism, vascular disease, technical errors, high hemoglobin level, thrombophilia, low albumin levels, malnutrition and inflammatory biomarkers affect this maturation process and can result in AVF failure.[5-10]

In vessels reduction in blood flow and oscillatory shear stress results in increased levels of inflammatory and pro-coagulant substances.[5] CRP that is an important Inflammatory marker, not only has a role in prediction of development of cardio vascular disease in patients undergoing HD. But its importance regarding development of vascular stenosis and thrombosis through the process of vascular intimal hyperplasia is also under discussion.[5] Fewer studies have been conducted with conflicting evidence to evaluate the effects of inflammatory biomarkers on AVF maturation[11,12]. We designed this study to evaluate relationship between preoperative raised CRP and AVF failure in ESRD patients.

Patients and Methods

All patients between January 2015 and March 2016, reporting to Vascular Surgery Clinic in Combined Military Hospital Lahore and Peshawar for AVF creation, were consecutively included in this study. Patients with uncontrolled diabetes (fasting blood sugar of more than 126mg/dl) and uncontrolled hypertension (blood pressure of more than 160/90 mmHg) were excluded. Serum CRP of all

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patients was checked in the hospital laboratory using Enzyme-Linked Immuno-Sorbent Assay (ELISA) method. CRP level more than 10mg/L was considered as positive value. Based on the serum CRP results, patients were assigned into two groups. Group A(Control) had all patients with normal CRP and Group B (Case) has patients with raised CRP. Other procedure related complications were also recorded.

All patients underwent AVF procedure by a Consultant Vascular Surgeon who had a minimum of five years of experience of doing such procedure under local anaesthesia. In order to remove the operator bias, the operating surgeon was kept unaware about the CRP status of the patient before and during the procedure. Patients were given oral antibiotics and analgesia on discharge. They were provided written instructions about hand and forearm exercises and general care of the AVF. Patients were regularly followed up in clinic at 2 weeks, 4 weeks, 2 months and 3 months. A functionally mature AVF is defined as per Kidney Disease Outcome Quality Initiative (KDOQI) guidelines as one that can be easily cannulated and has at least six successful consecutive dialysis sessions.[13] The failure rate and association with CRP was recorded.

The data was analyzed using Statistical Package for Social Sciences (SPSS) version 20. The numerical outcomes e.g. age was calculated as mean and standard deviation. Gender was recorded as frequency and percentage. Chi Square test was applied to assess the association between failure of fistula and qualitative variables like diabetes, hypertension and CRP. Independent t-test was applied to see the association between failure of fistula and quantitative variables like age. Logistic regression analysis was also done to assess the effect of age, gender, diabetes mellitus, hypertension and CRP on fistula failure rates. The results were considered statistically significant if the p value was found to be less than or equal to 0.05.

Results

Total 126 patients fulfilling the inclusion criteria were included in this study. The age range was 31 years - 64 years with mean age of 37.5±8.4 years. Out of 126 cases, 99 (78.5%) were males and 27 (21.4%) were females. Male to female ratio was 3.6:1. There were two groups: Group A (Control) had 62 patients with normal CRP and Group B (Case) had 62 patients with raised CRP. Among factors like, age (p value 0.754), gender (p value 0.867), diabetes (p value 0.812) and hypertension (p value 0.835); there was no statistically significant difference in the two groups (Table 1).

In Control group, 53 fistulae matured however in Case group only 29 AVF became functionally mature. Hence the failure rate was 14.5% in patients with normal CRP as compared to 53.2% in patients with raised CRP (Table 2). This difference between the two groups was statistically significant with a p value of 0.003.

Table 1: Comparison of variables between control and case groups

Variable	Group A (Control) n =62	Group B (Case) n =62	p value
Age(yrs) Mean±SD	38.1 ± 9.3	36.9 ± 7.8	0.754
Gender Male No (%)	47 (75.8)	52 (83.8)	0.867
Diabetic No (%)	42 (67.7)	39 (62.9)	0.812
Hypertensive No (%)	38 (61.2)	35 (56.4)	0.835

Table 2: Distribution of CRP in Control and Case groups

Group	Category	Number	Percentage
Group A N (62)	Failed	09	14.5
	Mature	53	85.5
Group B N (62)	Failed	33	53.2
	Mature	29	46.8

Table 3: Logistic regression analysis showing effect of different variables on fistula failure

Variable	B	SE	p value	Odd Ratio	95% Confidence Interval	
					Lower	Upper
Age	0.013	0.026	0.914	0.885	0.854	1.124
Gender	-0.294	0.526	0.794	0.726	0.384	1.754
Diabetes	-0.354	0.559	0.857	0.998	0.926	1.212
Hypertension	-0.261	0.591	0.932	0.869	0.442	1.954
CRP	2.985	0.416	<0.002	21.254	5.316	67.214

Logistic regression analysis of the variables was also done. The effect of age, gender, hypertension, diabetes mellitus and CRP was assessed on AVF failure. Only CRP had statistically significant effect on fistula failure rate with a p value of <0.002 (Table 3).

Discussion

HD in ESRD patients needs a vascular access. Vascular access can be achieved by a catheter insertion, arteriovenous graft or by creating a native AVF.[2-4] AVF is used for HD once it is matured functionally within 4-6 weeks.[14-16] Many factors like age, female gender, diabetes, hypertension, vessel diameter and hematological factors affect this process and can result in AVF failure.[16,17,11] In our study we specifically concentrated on association of inflammatory biomarker

Many studies suggest that inflammation causes intimal hyperplasia and higher chances of thrombosis at anastomotic site and hence responsible for failure of AVF.[11,12] Hence measuring inflammatory markers like CRP can point out

those patients who are at a higher risk of AVF maturation failure. Wong et al found for the first time that aggressive intimal hyperplasia at anastomotic site is associated with thrombotic closure of AVF thus pointing out inflammation as a culprit for higher AVF failure.[11] Neutrophil-lymphocyte ratio (NLR) is also a marker of systemic inflammation and is also used by certain studies as a benchmark to assess the association between inflammation and failure of fistula. Yilmaz et al in his logistic regression model has recently advocated that NLR is an independent positive predictor of AVF failure.[18]

Similar inference was also deducted by Roy-Chaudhury et al who found a strong positive association between inflammatory cell markers like CRP and fibrinogen, and failure of vascular access.[19] Chou et al suggested that elevated CRP is strong positive predictor for AVF thrombosis and they have found it as an independent risk factor for AVF failure.[12] Our study also shows that patients who had a higher levels of inflammation as evident from elevated CRP had higher rates of AVF failure. Kaygin et al in their study of 213 patients also found that high CRP levels in their patients who had failed AVF had significant impact.[20] A p-value of less than 0.001 was strongly suggestive of statistically significant effect of raised CRP on the fistulae failure rate. We have also found similar effect of raised CRP with a p-value of 0.003.

However, certain studies suggest that there is no relation of CRP levels and AVF failure. Meta-analysis by Morton et al in 2016 suggested that the current inflammatory biomarkers available are yet to identify the fistulas which are at risk.[21] Hence they have suggested that more robust biomarkers are needed which can predict the fistula failure rate. Similarly, Choice for Healthy Outcome In Caring for End stage renal disease (CHOICE) study by Banerjee et-al in 2010 reported higher failure of catheter related vascular access in patients with elevated CRP, however they did not find higher failure rates of AVF in patients with raised CRP levels.[22]

Low level of hemoglobin (Hb) is also thought to cause low grade inflammation and hence some workers have also labeled low Hb as a positive predictor for higher failure rates of AVF.[23,24] Hence those ESRD patients who have anemia may also be at a higher risk for failed AVF and probably CRP can be used as a marker to predict failure in such cases. We did not assess the Hb level and its association with CRP and AVF failure rate in this study.

Conclusion

Inflammation has a definite role in failure of AVF. Measurement of inflammatory markers like CRP can help in identifying those patients who are at high risk of access failure. We recommend further studies with larger sample size to define the exact role of inflammatory biomarkers.

Conflict of Interest

This study has no conflict of interest as declared by any author.

References

1. Lomonte C, Meola M, Petrucci I, Casucci F, Basile C. The key role of color doppler ultrasound in the work-up of hemodialysis vascular access. Semin Dial. 2015;28(2):211-5.
2. Tessitore N, Bedogna V, Verlato G, Poli A. The rise and fall of access blood flow surveillance in arteriovenous fistulas. Semin Dial. 2014;27(2):108-18.
3. Tessitore N, Bedogna V, Poli A, Lipari G, Pertile P, Baggio E, et al. Should current criteria for detecting and repairing arteriovenous fistula stenosis be reconsidered? Interim analysis of a randomized controlled trial. Nephrol Dial Transplant. 2014;29(1):179-87.
4. Almasi-Sperling V, Galiano M, Lang W, Rother U, Rascher W, Regus S. Timing of first arteriovenous fistula cannulation in children on hemodialysis. Pediatr Nephrol. 2016;31(10):1647-57.
5. Roy-Chaudhury P, Spergel M, Besarab A, Asif A, Ravani P. Biology of arteriovenous fistula failure. JNephrol. 2007;20(2):150-63.
6. Spergel M, Ravani P, Roy-Chaudhury P, Asif A, Besarab A. Surgical salvage of the autogenous arteriovenous fistula (AVF). J Nephrol. 2007;20(4):388-98.
7. Gagliardi M, Rossi S, Condino F, Mancuso D, Greco F, Tenuta R et al. Malnutrition, infection and arteriovenous fistula failure: is there a link? J Vasc Access. 2011;12(1):57-62.
8. Khavanin Zadeh M, Mohammadipour S, Omrani Z. Correlation between CRP and early failure of arteriovenous fistula (AVF).Med J Islam Repub Iran. 2015;29(8):1-5.
9. Ozdemir N, Akcay A, Bilgic A, Akgul A, Arat Z, Haberal M. Effects of smoking and blood eosinophil count on the development of arteriovenous fistulae thrombosis in hemodialysis patients. Transplant Proc. 2005;37(7):2918-21.
10. Vascular Access Work Group. Clinical practice guidelines for vascular access. vscular access work group. Clinical practice guidelines for vascular access. Am J Kidney Dis. 2006; S-1:S248-73.
11. Wong V, Ward R, Taylor J, Selvakumar S, How TV, Bakran A. Factors associated with early failure of arteriovenous fistulae for haemodialysis access. Eur J Vasc Endovasc Surg. 1996;12(2):207-13.
12. Chou Y, Kuo L, Yung F, Liu L, Huang C. C-reactive protein predicts vascular access thrombosis in hemodialysis patients. Blood Purificat. 2006;24(4):342–6.
13. Rayner C, Besarab A, Brown W, Disney A, Saito A, Pisoni L. Vascular access results from the dialysis outcomes and practice patterns study (DOPPS): Performance against Kidney Disease Outcomes Quality Initiative (K/DOQI) Clinical Practice Guidelines. Am J Kidney Dis. 2004;44(5 S-2):22–6
14. Rayner C, Pisoni L, Gillespie W, Goodkin A, Akiba T, Akizawa T, etal. Creation, cannulation and survival of arteriovenous fistulae: data from the dialysis outcomes and practice patterns study. Kidney Int. 2003;63(1):323–30.
15. Lok E, Oliver J, Su J, Bhola C, Hannigan N, Jassal V. Arteriovenous fistula outcomes in the era of the elderly dialysis population. Kidney Int. 2005;67(6):2462–69.
16. Conte S, Nugent M, Gaccione P, Roy-Chaudhury P, Lawson H. Influence of diabetes and perivascular allogeneic endothelial cell implants on arteriovenous fistula remodeling. J Vasc Surg. 2011;54(5):1383–9.
17. Salmela B, Hartman J, Peltonen S, Alback A,, Lassila R. Thrombophilia and arteriovenous fistula survival in ESRD. Clin J Am SocNephrol. 2013;8(6):962–8.

18. Yilmaz H, Bozkurt A, Cakmak M, Celik T, BilgicA, Bavbek N, et al. Relationship between late arteriovenous fistula (AVF) stenosis and neutrophil-lymphocyte ratio (NLR) in chronic hemodialysis patients. Ren Fail.2014;36(9):1390-4.
19. Roy-Chaudhury P, Arend L, Zhang J, Krishnamoorthy M, Wang Y, Banerjee R, et al. Neointimal hyperplasia in early arteriovenous fistula failure. Am J Kidney Dis 2007;50(5):782-90.
20. Kaygin A, Halici U, Aydin A, Dag O, Binici N, LimandalK, et al. The relationship between arteriovenous fistula success and inflammation. Ren Fail. 2013;35(8):1085-8.
21. Morton K, Rodríguez J, Morris R, Bhandari P, Moxon V, Golledge J. A systematic review and meta-analysis of circulating aiomarkers Associated with failure of arteriovenous fistulae for haemodialysis. PLoS One. 2016;11(7):e0159963.
22. Banerjee T, Kim S, Astor B, Shafi T, Coresh J, Powe N. Vascular access type, inflammatory markers, and mortality in incident hemodialysis patients: the choices for healthy outcomes in caring for End-Stage renal disease (CHOICE) study. Am J Kidney Dis. 2014;64(6):954–61.
23. Furuland H, Linde T, Ahlmen J, Christensson A, Strombom U, Danielson G. A randomized controlled trial of haemoglobin normalization with epopetin alfa in pre-dialysis and dialysis patients. Nephrol Dial Transplant. 2003;18(2):353-61.
24. Coronado Daza J, Martí-Carvajal AJ, Ariza García A, Rodelo Ceballos J, Yomayusa González N, Páez-Canro C, etal. Early versus delayed erythropoietin for the anaemia of end-stage kidney disease. Cochrane Database Syst Rev. 2015;12:CD011122..

Authorship Contribution:
Author 1: Conception, Synthesis and Planning of the research, Active participation in active methodology
Author 2 Active participation in active methodology, Interpretation, analysis and discussion
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