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Criteria for Successful Salvage of Failing Autogenous Hemodialysis Arteriovenous Fistulae Using balloon Angioplasty

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ABSTRACT

Background: Hemodialysis arteriovenous fistula dysfunction is a big challenging problem. Maintenance of this vascular access is one of corner stones in the care of patients with end stage renal disease. Ballooning angioplasty is the first line of salvage of failing arteriovenous fistula (AVF) due to stenosis of venous outflow. *Aim:* This prospective study aims at exploring factors affecting the outcome of ballooning angioplasty of failing arteriovenous fistula and postulating criteria for success of intervention. *Methods:* 40

patients with failing autogenous arteriovenous fistulae were recruited for percutaneous transluminal balloon angioplasty in the period from May 2018 to May 2019, follow up done for one year till May 2020. Technical & Clinical success rates were reported. The variables, including patients' demographics, co-morbidities, medications, fistula age, fistula type, site, number of lesions and degree of stenosis were analyzed and correlated with primary and secondary patency rates. *Results:* The median age of the AVF in this study since their creation was 24 months, we had 40 failing AVF: 16 (40%) radiocephalic AVF, 17 (42.5%) brachiocephalic AVF and 7 (17.5%) brachiobasilic AVF. The most common cause of autogenous AVF dysfunction was 90-99% stenosis while the most common site of stenosis was juxta-anastomotic (52.5%). Technical and clinical success rates of the study population were 97.5% and 95% respectively. The median postintervention primary and secondary patency during one year follow up were 6 and 12 months respectively. The primary patency at 1, 3, 6, 9, 12 months were 87.5%, 75%, 55%, 40% and 32.5% respectively. Univariate cox regression analysis of the variables that potentially affect success and patency of the procedure we found that three factors are associated with decrease both primary and secondary patency. Hyperlipidemia was associated with decrease primary patency with HR (95% CI) of 2.475 (1.034 – 5.926) and p-value of 0.042 and decrease in secondary patency with HR (95% CI) of 15.848 (1.839 – 136.586) and p-value of 0.012. Insulin intake was associated with decrease in primary patency with HR (95% CI) 3.531 (1.526 – 8.168) and p-value of 0.003 and decrease in secondary patency with HR (95% CI) 13.452 (1.563– 115.748) and p-value of 0.018. The presence of cephalic arch stenosis was also associated with decrease in primary patency with HR (95% CI) 4.950 (1.983 – 12.355) and p-value of 0.001 and decrease in secondary patency with HR (95% CI) 29.856 (3.418 – 260.795) and with p-value = 0.002. Multivariate cox regression analysis was done for the variables with significant association in univariate analysis (table 3) and found that primary patency was reduced by insulin intake with HR (95% CI) of 2.876 (1.200 – 6.889) and p-value of 0.018 and the presence of cephalic arch stenosis HR (95% CI) of 3.050 (1.158 – 8.030) and p value 0.024. And the secondary patency was found to be reduced only by the presence of cephalic arch stenosis HR (95% CI) of 17.794 (1.463 – 220.814) and p value 0.024. *Conclusion:* Ballooning angioplasty is an important method for salvage of failing hemodialysis arteriovenous fistula but the primary and secondary patency affected hugely by the site of stenosis (cephalic arch stenosis is associated with least primary and secondary patency); the use of some drugs as insulin decrease the primary patency. There is no proved association between medical comorbidities and patency.

Keywords: Hemodialysis autogenous arteriovenous fistula, failing arteriovenous fistula, vascular access salvage, cephalic arch stenosis, end stage renal disease.

1. INTRODUCTION

Vascular access is the life line for patients on hemodialysis. Most surgeons advocate the native arteriovenous fistula (AVF) to be the preferred vascular access because of its long term patency and less complication if compared to dialysis catheter or even synthetic arteriovenous graft (AVG) (Sidawy et al., 2008). Unfortunately there is a huge failure rate in AVF either failing to mature or failing after a period of usage. National Kidney Foundation Kidney Disease Outcomes Quality Initiative (NKF-K/DOQUI) adopts an aggressive maintenance protocol to preserve the AVF and keep it function successfully (Lok et al., 2020). Percutaneous balloon angioplasty is the main line of treatment of failing AVF due to stenosis of the venous outflow (Lok et al., 2020). The purpose of this clinical study is to determine factors that affect the success of the balloon angioplasty of the venous outflow of failing AVF.

2. PATIENTS AND METHODS

A prospective non randomized clinical study conducted at Ain shams university hospitals on 40 patients with failing autogenous arteriovenous fistulae recruited for percutaneous transluminal balloon angioplasty in the period from may 2018 to May 2019, follow up done for one year till may 2020.

Inclusion criteria:

Failing autogenous upper limb arteriovenous fistula detected through :

1-Reduced thrill of vascular access assessed by clinical palpation.

2-prolonged bleeding after removal of dialysis needle

3-increase dynamic venous pressure >300 mmHg

4-decrease dialysis flow rate to <400 ml/min.

5-more than 50% Stenosis detected by duplex ultrasound.

Exclusion criteria

1-Synthetic arteriovenous graft.
2-Immature or failed maturation of AVF.
3-Thrombosed or failed AVF.
4-Infected AVF.
5-stenosis of the arterial inflow.

Institutional approval from local ethics committee was obtained for this study, and formal informed consent was taken from all the participants in this study.

Procedural technique

Access to the AVF was gained by using micro puncture set (Cook, Bloomington, IN, USA). Following infiltration with local anesthetic agent using 2% lidocaine (Pfizer, Sydney, Australia), fistulography from the cannulation site to the right atrium was obtained by using intravenous contrast agent (Ultravist-300; iopromide 62.3%, 623 mg/mL, 300 mg/mL organically bound iodine; Bayer, Whippany, New Jersey). After completion of fistulography and determination of the site of the lesion we inserted a 6 french sheath over the wire after removal of the micro sheath. Conscious sedation with intravenous fentanyl citrate (100 µg/2 mL DBL; Hamelm, Germany) and midazolam HCL (5 mg/5 mL midazolam; Sandoz, Sydney, Australia) was achieved before balloon inflation. Standard guide wire (Terumo Corporation; Tokyo, Japan) was used to pass across the lesion. Most of the lesion passed by 0.035 but some tight lesion need 0.018 or 0.0014 guide wires. Ballooning was performed using 6-12 ml balloons. Standard balloon (admiral Xtreme; Medtronic, Minneapolis, MN, USA) or Intermediate-pressure (Mustang; Boston Scientific, Natick, Massachusetts) were used according to the operator and clinical situation. Balloon size was chosen by comparing with the adjacent segment of non diseased vein. A post procedure angiogram was then performed and balloon dilation was repeated for any residual stenosis greater than 30%. After intervention, a duplex was performed immediately after intervention to be repeated monthly during follow up period. The procedure that made a residual stenosis less than 30% will be defined as technically success.

Study endpoint and definitions

The following medical and personal data were recorded: patient age, sex, diabetes, hypertension, coronary artery disease, and hyperlipidemia.

Drug information was taken from the patient. The following drugs were recorded: beta blockers, calcium channel blockers, anti-platelet therapy, insulin, oral hypoglycemic and statins. Anatomic data recorded and analyzed were AVF age (time of creation of AVF to time of the need for first intervention), site (arm or forearm), degree of stenosis before angioplasty (as a percentage), residual stenosis (stenosis after angioplasty), lesion length, lesion site, and number of lesions if there is multiple lesions. Degree of stenosis before angioplasty was measured and recorded as a percentage and defined as the least diameter in comparison with the adjacent healthy nondilated vein just upstream of the lesion. Residual stenosis was measured and recorded in the same manner. For descriptive purposes, lesion location was classified into : anastomotic for lesions in arteriovenous anastomosis, juxta anastomotic for lesion within 2 cm of the anastomosis, puncture site for lesion involving puncture site in button hole puncture technique, midvein for lesion away from the anastomosis excluding puncture site, cephalic arch for lesion in cephalic vein where it traverse the clavipectoral facia and join axillary vein and finally central for the lesion in the central venous system from subclavian to superior vena cava.

Patency was defined as in Society of Interventional Radiology (SIR) reporting standards (Gray et al., 2003). Postintervention primary patency rate was defined as the percentage of the patent AVF after salvage by ballooning angioplasty until the need for repeating the angioplasty or thrombosis of the AVF. Postintervention secondary patency rate was defined as the percentage of the patent AVF after de-clotting of the previously angioplasty salvaged AVF either surgically by mechanical thrombectomy or percutaneously by thrombolysis until the AVF was surgically revised, or abandoned. Procedural complications were recorded and graded according to the SIR classification system (Sacks et al., 2003).

Statistical analysis

Categorial factors was described by frequencies and percentages while mean and standard deviation were used to describe continuous measure distributions. Kaplan–Meier curves were used to prescribe primary and secondary patency rates. Mann-whitny test was used to compare continuous variables. Variables and potential factors associated with post intervention primary and secondary patency were analyzed using univariate cox regression analysis to determine predictors and criteria of success of the

procedures. *P* values lower than 0.05 were considered significant. Multi variate cox regression analysis has done for all significant variables from univariate analysis to determine the final criteria of successful procedures.

3. RESULTS

Among the 40 cases, 22 were males (55%) and 18 were females (45%). Twenty-two (55%) of the patients were diabetics, 24(60%) patients were hypertensive, 7 (17.5%) patients hadcoronary artery disease, and 11 (27.5%) patients had hyperlipidemia. in the study population there were 18 (45%) patients on antiplatlets, 14 (35%) patients were on insulin, 7 (17.5) patients were on statins, 8 (20%) patients on metformin, 2 patients were on betablockers and 15 (37.5%) patients were on calcium channel blockers. Among the 40 stenotic fistulae, we have 16 (40%) radiocephalic AVF, 17 (42.5%) brachiocephalic AVF and 7 (17.5%) bracheobasilic AVF. The lesion was affecting the anastomosis in 4 (10%) cases, juxta anastomosis in 21(52.5%) cases, mid segment of the vein in 4 (10%) cases, puncture site in 6 (15%) cases, cephalic arch in 8 (20%) cases and affecting the central veins in 4 (10%) patients (Table 1).

Table 1 initial site of the lesion

Site of stenosis	Number of cases	Percentage
Central veins	4	10.0%
Cephalic arch	8	20.0%
Puncture site	6	15.0%
Mid vein	4	10.0%
Juxta anastomotic	21	52.5%
Anastomotic	4	10.0%

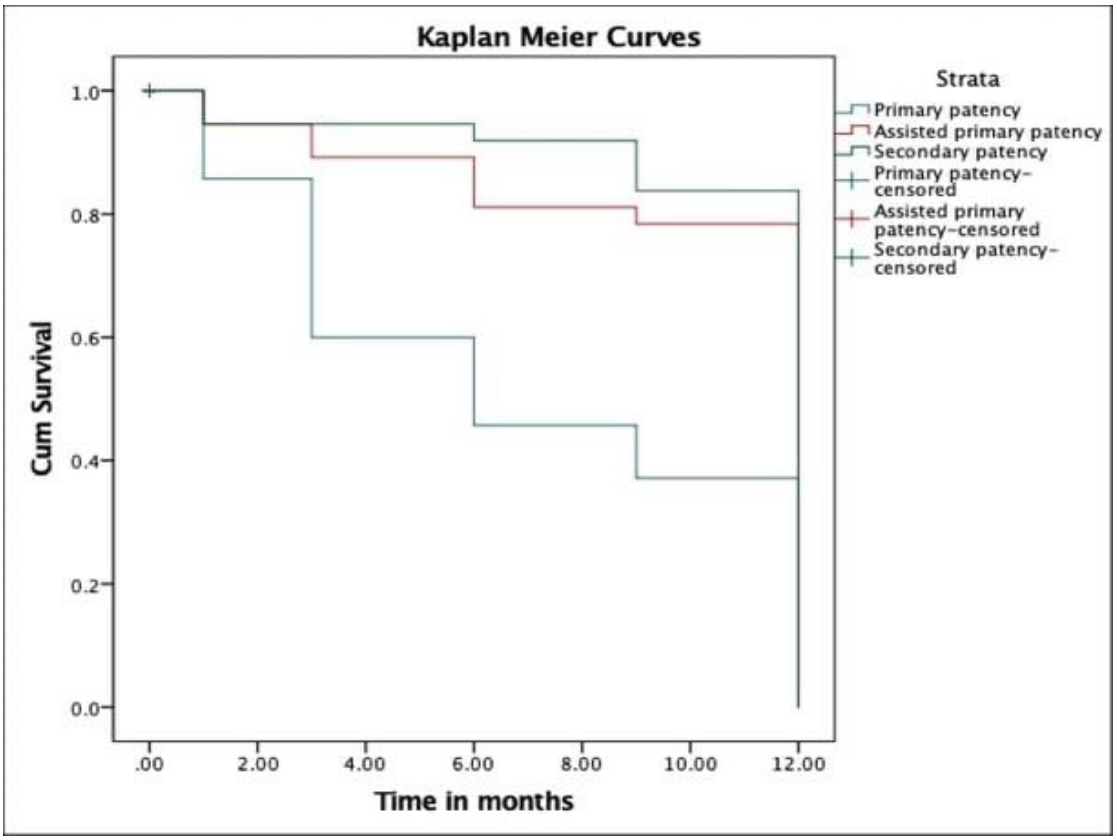

Figure 1 Kaplan–Meier estimate of postintervention primary, primary assisted and secondary patency after angioplasty.

The mean degree of stenosis before and after the angioplasty were 68% and 20% and the mean length of the stenosis was 5.44 cm. the age of the AVF in this study range from 5 to 120 months and the median age was 24 months. We use standard balloon in almost all patients and we need to use intermediate pressure balloon in 21 cases with tight and highly recoiled lesions failed to be

dilated with standard balloons. We documented minor complication in only one case with radial artery thrombosis which was asymptomatic and passed without the need for thrombectomy. And we documented major complication in only one case with axillary vein rupture during ballooning with 12 mm mustang balloon and significant bleeding need ligation of the AVF. As regard the access through which we did our procedures, we use radial artery in 34 (85%) cases, brachial artery in 4 (10%) cases and in the vein itself either antegrade in 1 (2.5%) case or retrograde in 1 (2.5%) cases. Technical and clinical success was 97.5% and 95% respectively. The median postintervention primary and secondary patency during one year follow up were 6 and 12 months respectively. The primary patency at 1, 3, 6, 9, 12 months were 87.5%, 75%, 55%, 40% and 32.5% respectively (figure 1). The primary assisted patency at 1, 3, 6, 9, 12 months were 92.5%, 87.5%, 82.5%, 75% and 72.5% respectively (figure 1). The secondary patency at 1, 3, 6, 9, 12 months were 92.5%, 87.5%, 87.5%, 85% and 77.5% respectively (figure 1).

In univariate cox regression analysis of the risk factors and anatomical factors of the AVFs (table 2) we found that three factors are associated with decrease both primary and secondary patency. Hyperlipidemia was associated with decrease primary patency with HR (95% CI) of 2.475 (1.034 – 5.926) and p-value of 0.042 and decrease in secondary patency with HR (95% CI) of 15.848 (1.839 – 136.586) and p-value of 0.012.Insulin intake was associated with decrease in primary patency with HR (95% CI) 3.531 (1.526 – 8.168) and p-value of 0.003 and decrease in secondary patency with HR (95% CI) 13.452 (1.563– 115.748) and p-value of 0.018. The presence of cephalic arch stenosis was also associated with decrease in primary patency with HR (95% CI) 4.950 (1.983 – 12.355) and p-value of 0.001 and decrease in secondary patency with HR (95% CI) 29.856 (3.418 – 260.795) and with p-value = 0.002.

Table 2 univariate Cox analysis of clinical and anatomical variables associated with post PTA primary and secondary patency

	Primary patency				**Secondary patency**			
	P-value	**HR**	**95.0% CI for HR**		**p-value**	**HR**	**95 5 CI for HR**	
			Lower	**Upper**			**lower**	**Upper**
Diabetes mellitus	0.059	2.315	0.970	5.527	0.206	69.529	0.097	49783.059
Hypertension	0.156	0.546	0.237	1.260	0.166	0.301	0.055	1.645
Hyperlipidemia	**0.042**	**2.475**	**1.034**	**5.926**	**0.012**	**15.848**	**1.839**	**136.586**
Coronary artery disease	0.940	0.954	0.282	3.226	0.250	2.710	0.496	14.812
Antiplatlets	0.221	0.571	0.233	1.400	0.852	1.164	0.235	5.771
Insulin	**0.003**	**3.531**	**1.526**	**8.168**	**0.018**	**13.452**	**1.563**	**115.748**
Statins	0.214	0.398	0.093	1.703	0.469	0.037	0.000	286.392
Type of access	0.476	1.207	0.720	2.022	0.380	1.581	0.568	4.401
Central vein	0.168	2.781	0.649	11.915	0.119	5.578	0.644	48.310
Cephalic arch	**0.001**	**4.950**	**1.983**	**12.355**	**0.002**	**29.856**	**3.418**	**260.795**
Puncture site	0.455	0.629	0.186	2.125	0.469	0.037	0.000	286.392
Mid-vein	0.576	1.416	0.419	4.785	0.615	0.043	0.000	9113.332
Juxta anastomotic	0.715	0.855	0.369	1.980	0.251	0.370	0.068	2.023
Anastomotic	0.390	0.415	0.056	3.083	0.661	1.617	0.189	13.860

Multivariate cox regression analysis was done for the variables with significant aass0cation in univariate analysis (table 3) and found that primary patency was reduced by insulin intake with HR (95% CI) of 2.876 (1.200 – 6.889) and p-value of 0.018 and the presence of cephalic arch stenosis HR (95% CI) of 3.050 (1.158 – 8.030) and p value 0.024. And the secondary patency was found to be reduced only by the presence of cephalic arch stenosis HR (95% CI) of 17.794 (1.463 – 220.814) and p value 0.024.

Table 3 multivariate cox analysis of significant clinical and anatomical factors associated with post PTA primary and secondary patency

	Secondary patency				**Primary patency**			
	P-value	**OR**	**95.0% CI for HR**		**p- value**	**HR**	**95.0%CIfor HR**	
			Lower	**Upper**			**Lower**	**Upper**
Hyperlipidemia	0.098	8.521	0.672	108.013	0.158	1.939	0.773	4.861
Insulin	0.109	8.133	0.628	105.392	**0.018**	**2.876**	**1.200**	**6.889**
Cephalic arch	**0.024**	**17.974**	**1.463**	**220.814**	**0.024**	**3.050**	**1.158**	**8.030**

4. DISCUSSION

Maintenance of the AVF is a vital process that affects the quality of life of the hemodialysis dependent people; because of the suboptimal primary patency of the AVF (Romann et al., 2016). Ballooning angioplasty of the failing hemodialysis AVF due to venous outflow stenosis is main line of treatment but unfortunately post PTA patency is still short reach 43% and 71% for primary and secondary patency respectively after one year (Kim et al., 2018).

In this clinical study we tried to study the efficiency of the ballooning angioplasty and see if there is a relationship between post PTA patency and different clinical and anatomical factors trying to postulate some criteria for successful salvage of failing hemodialysis AVF.

Juxta anastomotic lesions are the most common cause of failing AVF in our study population 52.5% which is the same as in other reports (Turmel-Rodrigues et al., 2000; Rajan et al., 2004). where juxta anastomotic lesions are found in 47-60% of patients presented with failing AVF but we found that the presence of cephalic arch stenosis is the most important lesion site associated with decrease both primary and secondary patency may be due to extrinsic compression by clavipectoral fascia that prevent vascular remodeling.

Cephalic arch stenosis is an important cause of failing brachiocephalic AVF, in our study we have 17 failing bracheocephalic AVF 47% of them are due to cephalic arch stenosis in which multivariate cox regression analysis shows a 3.050 -fold increased hazard for decreased post PTA primary patency and 17.974-fold increased hazard for decreased post PTA secondary patency. So many of trials suggest other modalities in treatment of cephalic arch stenosis because of high rate of recurrence and decrease both primary and secondary patency in ballooning angioplasty as in randomized control trial by Shemesh et al. which examined the role of stenting in cephalic arch stenosis by stent graft and its superior primary and secondary patency over ballooning angioplasty (Shemesh et al., 2008).

And other trials studied surgical intervention as a good option for cephalic arch stenosis which show a superior patency over percutaneous intervention especially in young fit patients (Davies, Haider, and ElSayad., 2016).

Diabetes mellitus by itself was not associated with decrease post PTA primary or secondary patency but Insulin intake had 2.876-fold increased hazard for decreased post PTA primary patency. This may be justified by the fact that using insulin is almost associated with uncontrolled long standing diabetes but patient use oral hypoglycemic medication in controlled diabetes. But in literature there is no evidence that diabetes or insulin intake affect vascular access patency (Baktiroglu et al., 2016).

Some studies reported dyslipidemia as factor associated with decrease post PTA secondary patency (Kim et al., 2018). But in our study multivariate cox regression analysis found no significant association between dyslipidemia and primary or secondary patency.

In our study, there is no medication except insulin proved to have effect on the patency after balloon angioplasty of failing autogenous AVF. However the use of antiplatelets a (Nikam et al., 2015; Palmer et al., 2013) and statins (Tonelli et al., 2008) for the beneficial effects on vascular smooth muscle and the prevention of thrombosis has been described variably in human and animal studies, but there are other studies found no similar association (Neuen et al., 2014).

We had some limitations in this study that should be acknowledged. The most important limitation is the relatively small number of the patient, so some factors that could affect the success of our procedure could not fully analyzed. The most important factor that could not fully analyzed with significant data is the age of AVF.

A lot of studies postulate the age of the AVF as an independent factor affect the patency of the angioplasty salvaged AVF and found that AVF age less than 6 month is associated with decrease both primary and secondary patency (Neuen et al., 2014). But we could not assess this factor because we only have one case with AVF age less than 6 month and the median AVF age in our study population was 24 months.

5. CONCLUSION

In conclusion Ballooning angioplasty is an important method for salvage of failing hemodialysis arteriovenous fistula but the primary and secondary patency affected hugely by the site of stenosis (cephalic arch stenosis is associated with least primary and secondary patency), the use of some drugs as insulin decrease the primary patency. There is no proved association between medical comorbidities and patency.

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Details of contribution of each authors regards manuscript work & production.

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Conflict of Interest: The authors declare that there are no conflicts of interests.

Informed consent: Written & Oral informed consent was obtained from all individual participants included in the study.

Ethical approval: The study was approved by the Medical Ethics Committee of Department of General Surgery, Faculty of Medicine, Ain shams University, Cairo, Egypt Code (No.IRB 00006379).

Data and materials availability: All data associated with this study are present in the paper.

Peer-review
External peer-review was done through double-blind method.

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