Pulse Thrombolysis of Thrombosed Arterio-Venous Access Using Different Doses of Recombinant Tissue Plasminogen Activator

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Background: Thrombosis of arterio-venous access (AVA) is a common complication. Pulse thrombolysis for AVA followed by angioplasty yields high technical success rates, however, there is no consensus about thrombolytic agent or dose to be used.

Pathients and methods: All patients who underwent AVA thrombolysis between July 2022 and June 2023 were included. The primary outcome was primary patency. Secondary outcomes were assisted primary patency, mortality and procedure related complications. Patients were divided randomly into two equal groups. Group I received 6mg of rt-PA for pulse thrombolysis while Group II received 10mg. All patients had angioplasty of stenosed segments following thrombolysis.

Results: Thirty-two patients underwent AVA thrombolysis during the study period with a mean follow-up period of 32.13 weeks +/- 6.84 SD (30.44 weeks in Group I and 33.81 in Group II).
After six weeks the primary patency clinically in Group I was 81.25% while it was 93.75% in Group II -P value 0.29- while after six months it was 50% in Group I and 81.25% in Group II –P value 0.063.
Assisted primary patency in Group I after six months was 56.25% while it was significantly higher in Group II 87.5% –P value 0.05.

Conclusions: Pulse thrombolysis using rt-PA has a high technical success rate. Using higher dose of rt-PA yield higher rate of primary patency but significantly higher in assisted primary patency after six months. Using the higher dose of thrombolytic agent was not associated with higher mortality or procedure related complication during the study follow up period.

Key words: Arteriovenous access, pulse thrombolysis, patency, recombinant tissue plasminogen activator.

Introduction

It is well established that mature arterio-venous fistula (AVF) is the best durable and well-tolerated method for haemodialysis (HD) followed by arterio-venous graft (AVG).[1] The most common complication, which encounters these arterio-venous axes (AVA), is thrombosis.[2]

There are multiple techniques described to salvage a recently thrombosed AVA.[3] One of them is pulse thrombolysis followed by angioplasty of any stenosed segment along the AVA.[4] This technique has a high technical success rates, but there is no consensus about the dose and the type of thrombolytic agent, how late we can salvage the thrombosed AVA and the long-term outcomes.

We conducted a study to compare the efficacy and safety of using two different doses (6mg versus 10mg) of recombinant tissue plasminogen activator (rt-PA) to perform pulse-spray thrombolysis of thrombosed hemodialysis access.

Pathients and methods

The research ethics board at Ain Shams University, Cairo, Egypt approved this study. All patients with AVA dysfunction for less than 2 weeks were identified in the dialysis unit by a hemodialysis nurse or a nephrologist and were referred to our vascular unit in Ain Shams University. Patients underwent clinical assessment -history taking and clinical examination, laboratory tests and ultrasound evaluation to diagnose AVA thrombosis and exclude proximal arterial stenosis prior to intervention.

We have excluded all patients who had a thrombosed AVA before maturation or was never used for HD, patients with a bleeding tendency, allergy towards iodine based contrast media, heparin or rt-PA, thrombocytopenia if platelet count is less than 100,000 platelets per microliter of blood or infection of the skin over the thrombosed AVA. Patients with pulmonary hypertension and known right-left intra-cardiac shunts were excluded too due to the potential risk of embolization.

All patients undergoing thrombolysis were informed about the risks of the procedure -including: failure, bleeding, haematoma formation, infection, pulmonary embolism, heparin induced thrombocytopenia, steal syndrome and venous perforation- and provided informed consent.

A temporary HD catheter was inserted away from the limb that will be treated –if possible- and a full HD session less than 24 hours prior to the thrombolysis was done.

We have included all patients who underwent AVA thrombolysis between July 1, 2022 and June 30, 2023 at two academic hospitals of Ain Shams University. We were able to perform the procedure

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for 32 patients who had been divided randomly into two equal groups by closed envelopes method and followed up post-operatively for 6 months at least. Group I -16 patients- has received 6 mg of rt-PA pulse thrombolysis while Group II -16 patients- has received 10 mg of rt-PA. The procedures were performed in theatre under local anesthesia and sedation using midazolam during balloon angioplasty.

The AVA was accessed using ultrasound guidance, with 14 or 16 Gauge needle puncture of the AVA just proximal to the arterial anastomosis **(Fig. 1)**. The position of the needle was confirmed by U/S and injection of 2-4cc of normal saline to see the saline flowing inside the AVA by the U/S before injecting the thrombolytic agent.

This was followed by injection of pulses of rt-PA in the form of either 6 mg in the Group I or 10 mg in Group II (1mg/min) **(Fig. 2)** followed by a bolus of 5000 units of Heparin in AVA while patient is monitored then we have waited for 30 minutes.

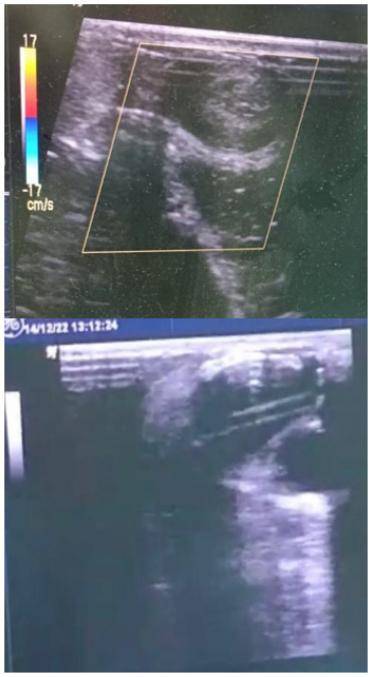

Fig 1: An ultrasound image of a thrombosed AVA (Above), Ultrasound guided insertion of an IV Line for rt-PA injection (Below).

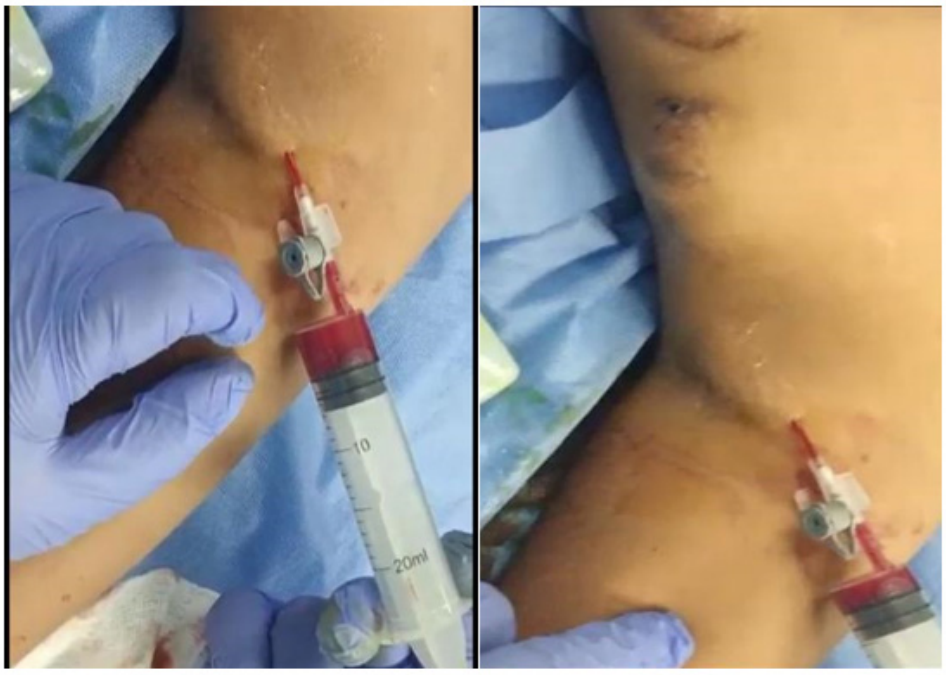

Fig 2: Pulse injection of rt-PA in the thrombosed AVA.

This was followed by exchange of the needle with 6 F sheath. 0.035 hydrophilic 260cm guide wire (GW) floppy angled tip was advanced under U/S and/or C-arm fluoroscopy guidance. Angiogram is done through the sheath to visualize all the veins from the access up to superior vena cava (SVC) to identify thrombus load, kinks, aneurysms, stenosed venous segment and central veins status. In some cases due to AVA aneurysm, kink or tight stenosis we had to use a Bern 4F catheter to direct the wire towards SVC.

The stenosed segment was dilated using appropriate balloon size according to vein diameter –Figure 3-. Balloon maceration of the clot was performed if needed using 6mm-8mm balloons of high-pressure (Mustang- Boston scientific®), starting at the central end of the clot. In cases had remnants of clots along the AVA, these were pushed from distal to proximal towards central veins using a semi-inflated balloon. Central venous stenosis was dilated using appropriate high-pressure balloons without stent placement.

Afterwards, another 6F sheath was inserted under U/S guidance towards the arterial anastomosis, 15 cm at least proximal to it. The GW and either a balloon or a catheter that was used previously was advanced under fluoroscopy to be placed in the artery feeding the AVA to perform an angiogram to exclude stenosis of the arterial anastomosis. If present, it was treated using 5-6mm high-pressure balloon angioplasty. Final angiogram was done to ensure there is no residual significant stenosis along the AVA from the arterial anastomosis distally to SVC proximally at the end of the procedure.

Hemostasis at the site of sheath insertion is achieved using purse string sutures around it.[5]

The patient was transferred to the recovery room/ surgical ward and monitored for 4 hours prior to discharge.

Clinical success was confirmed by the restoration of the AVA thrill and/or pulse. This was confirmed radiologically by intra-operative angiogram with or without U/S duplex. Post procedure technical success was defined as substantial relief of stenosis or occlusion and restoration of flow with residual narrowing of 30% or less, significant hemodynamic improvement, and no major morbidity (British Institute of Radiology, 2020).

On the following 48 hours post procedure all patients had another session of HD either from a temporary HD catheter or from the treated AVA.

The primary outcome was post-procedure primary patency defined as AVA survival without re-intervention including angioplasty ± stent with/ without re-thrombolysis. Secondary outcomes were post-procedure assisted primary patency defined as AVA survival until re-thrombosis requiring re-intervention to salvage the AVA, occurrence of any complication and mortality. These definitions are based on the Society of Vascular and Interventional Radiology Quality Improvement Guidelines,[6] and the American Society of Nephrology and US Food and Drug Administration Kidney Health Initiative.[7]

All patients were followed up at least six months post procedure. The follow up was done either by clinical examination to palpate pulse and/or thrill over the AVA, and to identify the presence of any complication/ mortality and/or taking history about HD session from the dialysis team. We have liaised with HD staff and patients to collect data about time between procedure and first HD session done from the treated AVA, efficiency of HD sessions from it and any difficulty encountered during HD post procedure.

Statistical analysis

We compared patient characteristics, access criteria and procedure outcome between the 2 groups. All continuous data were presented as mean ± standard deviation using Student's t-test. Categorical data were evaluated by chi-square test. Patency rates between the 2 groups were analysed by the Kaplan-Meier test. P values less than 0.05 were considered to be statistically significant.

Results

Patient characteristics

We have treated 32 patients with a recently thrombosed AVA (Less than 2 weeks) with pulse thrombolysis using rt-PA followed by access angioplasty. Patients were divided into two groups, Group I received 6 mg of rt-PA for thrombolysis while Group II received 10 mg. Patients were allocated randomly into the two groups using closed envelopes (16 patient in each group).

Table 1 shows the different demographics of the patients. Age did not differ significantly between the two treatment groups -46.5 in Group I and 48.75 in Group II- (P= 0.63) There were less females in the both groups -25% in Group I and 37.5% in Group II- but this difference was statistically insignificant (P= 0.45) Both groups had similar number of diabetic patients, but there were more patients with hypertension in Group I, while there were more smokers and patients with ischaemic heart disease in Group II with no significant difference between both groups among these characteristics **(Table 1).**

Most of our patients were right handed & had the thrombosed AVA in their left upper extremity. Less than 25% of the patients had a thrombosed prosthetic graft and most of the thrombosed AVA was not the first access the patient had. Our cohort of patients had HD for years before thrombosis of

the access. There was no statistically significant difference among these characteristics between both groups but duration of dialysis was longer in Group II (P value 0.19) **(Table 2).**

The duration of function of the thrombosed AVA was slightly longer in Group II 31.9 months versus 24.3 in Group I (P value 0.24). All patients had the thrombolysis procedure within 12 days of thrombosis (Mean 4.8 days in Group I and 4 days in Group II –P value 0.38-. Two patients in Group II had their initial surgery side-to-side anastomosis. **(Table 3).**

Table 4 shows the site of AVA stenosis, most patients had some degree of stenosis either along the fistula vein –cephalic or basilic- or graft or in central veins. Few patients had significant arterial and/or venous anastomosis stenosis. Any stenosis more than 30% -diagnosed by intra-procedure angiogram- was treated with angioplasty using the appropriate size high-pressure balloon. **(Table 4).**

There was no statistically significant difference between both groups regarding procedure time and blood loss. Procedure time in Group I was 41.25 minutes while 42.5 in Group II (P value 0.8). Blood loss was higher in in group II 49.69 mg in comparison to 43.13 mg in Group I (P value 0.59) **(Table 5).**

All our patients had no thrill prior to the procedure over their AVA. Most of patients have regained a clinically palpable thrill one day post-procedure (68.75% in Group 1 and 81.25% in Group 2 (P value 0.41) and more patients regained thrill one week post-procedure (75% in Group 1 and 93.75% in Group 2 –P value 0.14-) **(Table 6).**

By ultrasound all patients regained flow in their AVA immediately after the procedure but two patients had no flow in the access in Group I one week post-procedure.

Following the procedure, patients who had a successful AVA salvage had a HD session from the treated access after 2.77 days in Group I and 2.73 days in Group II –P value 0.18-. More than 80% of patients had a successful HD session from the treated AVA, 81.25% in Group I and 93.75% in Group II (P value 0.29).

We had three cases that had a post-procedure bleeding (Two in Group I and one in Group II) and two cases of access related subcutaneous haematoma (One in each group). But none of these patients needed blood transfusion post-procedure or re-intervention. We didn't have any case of infection or steal syndrome or symptomatic pulmonary embolism.

After six weeks the primary patency clinically in Group I was 81.25% while it was 93.75% in Group II -P value 0.29- while after six months it was 50% in Group I and 81.25% in Group II (P value 0.063) **(Figure 4, Table 7).**

Assisted primary patency in Group I after six months was 56.25% while it was significantly higher in Group II 87.5% (P value 0.05) **(Figure 5, Table 8**).

We have lost three patients because of mortality (Two in Group I and one in Group II –P value 0.54). None of these mortalities was related to AVA complication.

Among our study period we have followed the patients for mean of 32.13 weeks +/- 6.84 SD (30.44 weeks in Group I and 33.81 in Group II –P value 0.17-).

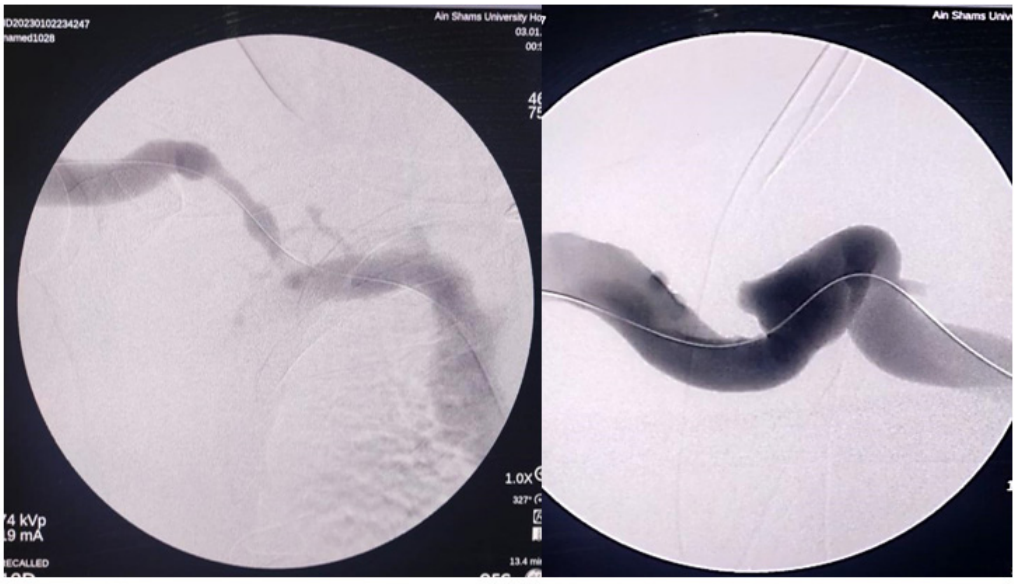

Fig 3: Angioplasty of cephalic arch following AVA thrombolysis.

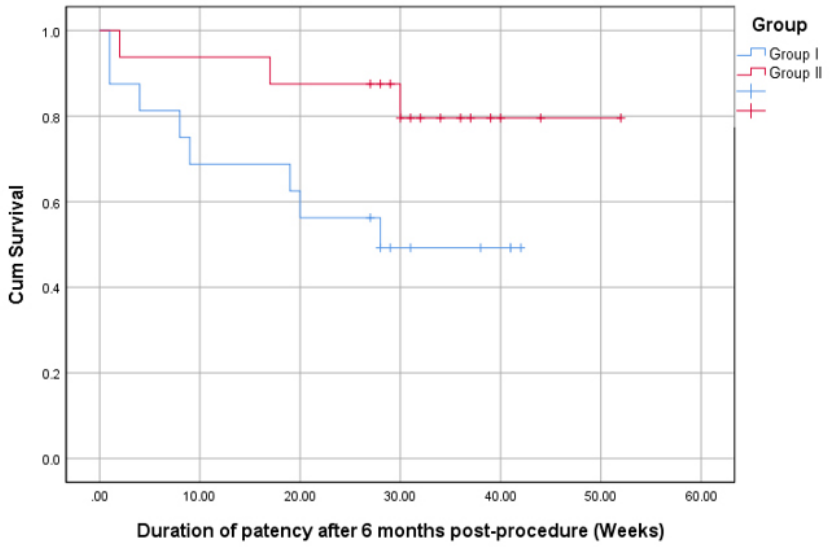

Fig 4: Kaplan-Meier curve of primary patency following AVA thrombolysis.

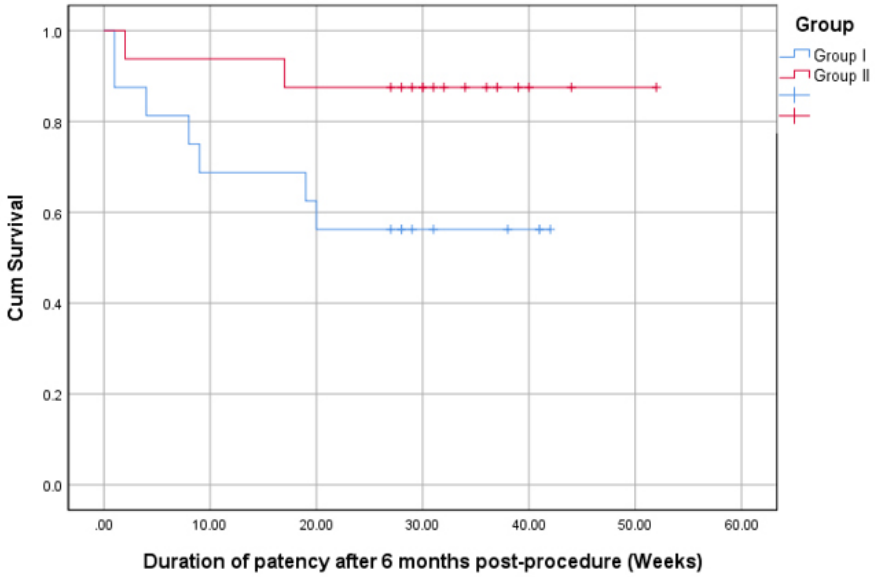

Fig 5: Kaplan-Meier curve of assisted primary patency following AVA thrombolysis.

Table 1: Demographics of patients in both groups

Demographic data		Group									T-Test	
		Group I			Group II			Total			t	P-value
Age (Years)	Range	20	-	64	24	-	64	20	-	64	-0.48	0.63
	Mean ±SD	46.50	±	12.31	48.75	±	14.00	47.63	±	13.02		
Chi-Square		N		%	N		%	N		%	X^2	P-value
Gender	Male	12		75.00	10		62.50	22		68.75	0.58	0.45
DM		6		37.50	6		37.50	12		37.50	0.00	1.00
HTN		9		56.25	12		75.00	21		65.63	1.25	0.26
IHD		2		12.50	1		6.25	3		9.38	0.37	0.54
Smoking		4		25.00	3		18.75	7		21.88	0.18	0.67
Other diseases		2		12.50	2		12.50	4		12.50	0.00	1.00

Table 2: Comarison between the two groups regarding longevity of ESRD, dominant hand and characters of AVA

		Group						T-Test	
		Group I		Group II		Total		t	P-value
Time since diagnosed as ESRD (Months)	Range	8 - 72		20 - 240		8 - 240		-1.34	0.19
	Mean ±SD	37.63± 19.35		56.13 ± 51.71		46.875 ± 39.540			
Chi-Square		**N**	**%**	**N**	**%**	**N**	**%**	**X^2**	**P-value**
Dominant hand	Right	14	87.50	13	81.25	27	84.38	0.24	0.63
Nature of AV access conduit material	Autogenous	13	81.25	12	75.00	25	78.13	0.18	0.67
Location of AVA	Left UL	13	81.25	10	62.50	23	71.88	1.39	0.24
Previous procedures same limb	No prior procedures	4	25.00	6	37.50	10	31.25	0.67	0.88
	One prior procedure	8	50.00	7	43.75	15	46.88		
	Two prior procedures	3	18.75	2	12.50	5	15.63		
	Three or more prior procedures	1	6.25	1	6.25	2	6.25		

Table 3: Duration of AVA function prior to thrombosis and interval between thrombosis and thrombolysis

		Group						T-Test	
		Group I		Group II		Total		t	P-value
Duration of function of AVA (Months)	Range	5 - 48		3 - 96		3 - 96		-1.21	0.24
	Mean ±SD	24.25 ± 12.62		31.88 ± 21.82		28.06 ± 17.95			
Time from thrombosis till procedure (Days)	Range	1 - 12		1 - 7		1 - 12		0.89	0.38
	Mean ±SD	4.81 ± 3.02		4.00 ± 2.10		4.41 ± 2.59			
Chi-Square		**N**	**%**	**N**	**%**	**N**	**%**	**X^2**	**P-value**

Table 4: Stenosis site based on intra-procedure angiogram

Venographic site of stenosis (Stenosis, >50% in diameter)	Group						Chi-Square	
	Group I		Group II		Total			
	N	**%**	**N**	**%**	**N**	**%**	**X^2**	**P-value**
Arterial anastomosis	1	6.25	0	0.00	1	3.13	1.29	0.52
Intra graft or vein	1	6.25	2	12.50	3	9.38	0.42	0.81
Central veins	5	31.25	6	37.50	11	34.38	0.23	0.89
Venous anastomosis	0	0.00	2	12.50	2	6.25	2.24	0.33

Table 5: Procedure time and blood loss

		Group			T-Test	
		Group I	Group II	Total	t	P-value
Estimated procedure time (Minutes)	Range	25 - 75	25 - 70	25 - 75	-0.26	0.80
	Mean ±SD	41.25 ± 13.96	42.50 ± 13.17	41.88 ± 13.37		
Estimated blood loss during operation. (ml)	Range	20 - 100	25 - 200	20 - 200	-0.55	0.59
	Mean ±SD	43.13 ± 24.35	49.69 ± 41.45	46.41 ± 33.61		

Table 6: Presence of a clinically palpable thrill post procedure

Thrill (Palpable thrill felt)		Group						Chi-Square	
		Group I		Group II		Total			
		N	%	N	%	N	%	X^2	P-value
Pre		0	0.00	0	0.00	0	0.00	-	-
Immediate		11	68.75	4	25.00	15	46.88	6.15	0.01*
1 Day post procedure		11	68.75	13	81.25	24	75.00	0.67	0.41
1 Week post procedure		12	75.00	15	93.75	27	84.38	2.13	0.14
P-value	Pre-IM	<0.01*		0.11		<0.01*			
	Pre-P 1D	<0.01*		<0.01*		<0.01*			
	Pre-P 1W	<0.01*		<0.01*		<0.01*			

Table 7: Primary patency after six weeks and six months

		Group						T-Test	
		Group I		Group II		Total		t	P-value
Duration of patency after 6 months post-procedure (Weeks)	**Range**	1 - 42		2 - 52		1 - 52		-1.92	0.07
	Mean ±SD	22.94 ± 14.55		31.75 ± 11.21		27.34 ± 13.54			
Chi-Square		N	%	N	%	N	%	X^2	P-value
Follow up six months post procedure -primary patency		8	50.00	13	81.25	21	65.63	3.463	0.063

Table 8: Assisted primary patency after six months

After redo procedure -assisted primary patency	Group						Chi-Square	
	Group I		Group II		Total			
	N	%	N	%	N	%	X^2	P-value
No	7	43.75	2	12.50	9	28.13	3.87	0.05*
Yes	9	56.25	14	87.50	23	71.88		

Table 9: Clinical indicators (Signs and symptoms) suggesting underlying clinically significant lesions during access monitorin[9]

Procedure	Clinical Indicators
Physical examination or check	Ipsilateral extremity edema
	Alterations in the pulse, with a weak or resistant pulse, difficult to compress, in the area of stenosis
	Abnormal thrill (weak and/or discontinuous) with only a systolic component in the region of stenosis
	Abnormal bruit (high pitched with a systolic component in the area of stenosis)
	Failure of the fistula to collapse when the arm is elevated (outflow stenosis) and lack of pulse augmentation (inflow stenosis)
	Excessive collapse of the venous segment upon arm elevation
Dialysis	New difficulty with cannulation when previously not a problem
	Aspiration of clots
	Inability to achieve the target dialysis blood flow
	Prolonged bleeding beyond usual for that patient from the needle puncture sites for 3 consecutive dialysis sessions
	Unexplained (>0.2 units) decrease in the delivered dialysis dose (Kt/V) on a constant dialysis prescription without prolongation of dialysis duration

Discussion

Thrombosis of a mature AVA leads to multiple missed HD sessions, frequent admission and the necessity to insert a temporary dialysis catheter with all the potential hazards involved. It is estimated that 65–85% of cases of permanent access loss are due to AVA thrombosis.[2]

Prior to AVA thrombosis, occurrence of any clinical sign that might indicate AVA malfunction as shown in table 91 or discovery of any significant stenosis in surveillance by ultrasound should be considered for endovascular angioplasty of stenotic lesion(s).[8-10]

A study done in 2022 has showed that pre-emptive angioplasty for AVA dysfunction carries less risk, costs less and has a better primary, assisted primary and secondary patency in comparison to post-thrombotic percutaneous endovascular intervention for thrombosed AVA despite both had 100% technical success.[11]

Each AVA nowadays should be considered precious1. In cases of AVA thrombosis, if patient accepts risks and the access was thrombosed recently, AVA salvage should be tried. Different approaches were described including surgical thrombectomy, endovascular procedures (Pharmacological, mechanical & pharmaco-mechanical) and hybrid techniques. Generally speaking endovascular approach seems to be more effective and tolerable by patients but endovascular mechanical and pharmaco-mechanical procedures are associated with a major drawback, which is their high cost.[12] Thrombolysis followed by angioplasty is one of these techniques. There is no consensus about one superior technique and no agreement as well about the type and dose of thrombolytic agent.

In our study we have adopted the technique of pulse rt-PA infusion -1 mg per minute injection- for thrombosed AVA using either 6 or 10 mg followed by AVA angioplasty. Our patients were referred to us and intervention was done in less than two weeks.

Koraen-Smith et al,[13] compared surgical thrombectomy versus catheter directed thrombolytic infusion. They have treated 131 patients with 149 episodes of AVA thrombosis (107 surgical thrombectomy and 42 thrombolysis). In thrombolysis group the technical success was 74% -was 62% in surgical thrombectomy group-. The rt-PA was used as a thrombolytic agent till patency was re-established. In patients with large thrombus burden AV access angioplasty was done. This study didn't comment on the time interval between thrombosis and intervention. Our technical success instantly after the procedure was much higher than Koraen-Smith et al study. This might be understood if there was longer interval between thrombosis and intervention in Koraen-Smith et al. After 1 week AVA patency in Group I in our study was similar to

the thrombolysis group in their study 75% versus 74%. They have concluded that thrombolysis had a better-assisted primary patency in thrombosed AVA.

In a study published in 2019, Tan et al,[14] compared the use of rt-PA versus urokinase for thrombosed AV access. The study showed that urokinase versus rt-PA clinical success rate was (88.7% versus 97.1%) while our technical success instantly was 100% using our technique. But one week post procedure it was 75% in Group I and 93.75% in Group II. Ten et al primary patency rates at 3 months (57.1% versus 70.1%) while our rate after 6 months were 50% in Group I and 81.25% in Group II. Thrombosis-free survivals of the vascular access were 113.2 days versus 122 days. All these parameters were in favor of rt-PA but not statistically significant. Procedure time, fluoroscopy time, skin dose, and dose of contrast were significantly less when rt-PA was used.

Li et al,[15] have conducted a study in Canada and published in 2021, gathered patients with thrombosed AVG between January 2005 & December 2015. They treated the patients with injecting 6ml of rt-PA and 3000U IV heparin in the thrombosed segment followed by over the wire Fogarty catheter thrombectomy and aspiration of the thrombus from the sheath sidearm. This pharmacomechanical thrombus removal was followed by angioplasty of the stenotic segment related to the AVG. They have treated 74 thrombosed AVG with 96% technical success, which is similar to our technical success despite we didn't do mechanical thrombectomy using a Fogarty's catheter in our study. Li et al study didn't specify the time interval between the thrombosis and performing the procedure. The primary patency of this technique at 1,3 and 5 years were 43.2%, 20.2% and 7.7% respectively in comparison to our six months collective primary patency of 65.6% -50% in Group I and 81.25% in Group II-. Their cumulative patency at 1,3 and 5 years were 75%, 38.8% and 22.6% in comparison to our six months collective assisted primary patency of 71.88% -56.25% in Group I and 87.5% in Group II-. The study didn't comment on complications of thrombolytic therapy.

In 2006 a study done by Cho on fourteen patients who had thrombosis of native AVFs underwent percutaneous restoration following 20 episodes of thrombosis,[16] all patients except one were treated with urokinase injection utilizing the pulse-spray technique and had subsequent balloon angioplasty. One patient was treated by percutaneous angioplasty alone.

Our technique we have adopted was very similar to this study technique but we have used rt-PA instead of urokinase.

Cho et al study showed technical and clinical success were achieved in 15 (75%) of 20 AVFs. Four of the five technical failures resulted from a failure to cross the occluded segment. Including the initial technical failures, primary patency rates at six and 12 months were 64% and 55%, respectively. Secondary patency rates at six and 12 months were 71% and 63%, respectively. Our overall assisted primary patency was 71.88% -56.25% in Group I and 87.5% in Group II.

Hongsakul et al,[17] have examined 108 patients with 114 thrombosed dialysis grafts during a 3-year period from January 2009 to December 2011, referred for treatment. Fifty thrombosed dialysis grafts underwent pulse-spray catheter thrombolysis using rt-PA with angioplasty, and 64 thrombosed dialysis grafts underwent surgical thrombectomy.

The study found no differences in outcomes between patients treated with pharmacomechanical thrombolysis and patients treated with surgical thrombectomy for thrombosed haemodialysis grafts. Additionally, there were no procedure-related major complications in the patients treated with pharmacomechanical thrombolysis, indicating that pharmacomechanical thrombolysis is a safe and effective procedure.

Hongsakul et al have used a total dose of 10 mg of rt-PA 4 mg of loading dose via infusion catheter and forceful injections of 0.5 mg of rt-PA via infusion catheter every 30 seconds. Balloon angioplasty was performed to macerate the residual clots and treat all underlying stenoses. A final angiogram was done to assess the patency graft, arterial and venous anastomoses, venous outflow and central veins. Thrombectomy was performed by advancing a Fogarty thrombectomy catheter.

The primary patency rates at 12 months in their study was 28.0% ± 8.4% for the thrombolysis group. We had a better primary patency at six months. Their low 1 year primary patency might be explained by longer follow up, treating AVG only and/or treating some patients later than we have treated ours.

Stanley Cooper,[18] in 2003 has treated 17 patients with acutely thrombosed AVG with thrombolysis using pulse spray technique with an average dose of 2 mg over a mean period of 16 minutes. Technical and clinical success was achieved in 16 (94%) of 17 procedures. No complications were recorded in this series of procedures. Successfully treated grafts remained patent for a mean of 72 days. Primary patency was 71% at 30 days and 47% at 90 days. He had less primary patency than our study and this is expected if he didn't try to identify and treat the culprit lesion that led to thrombosis.

A study conducted by Sofocleous et al,[19] from November 1999 to May 2001, 68 episodes of occlusion in 50 grafts (In 49 patients) were included

in this study. Occlusion was treated with pulse-spray (N =41) or lyse-and-wait (N= 27) thrombolysis with use of rt-PA, and balloon angioplasty of all identified stenoses was performed. The arterial plug was mobilized with the Fogarty maneuver. Procedural success was achieved in 94% episodes with variable doses of rt-PA -2–10 mg (Mean= 4.13 mg)-, allowing successful hemodialysis within 24 hours. Primary patency rate was 72% at 30 days in comparison to 87.5% -81.25% in Group I and 93.75% in Group II- in our study six weeks post procedure. While after six months their primary patency was 44% in comparison to 65.66% in our study.

Sofocleous et al study showed major complications in seven cases (10.3%). These included two incidents of bleeding, one incident of non-retrievable occlusive broken balloon fragment; two arterial emboli; and two cases of balloon rupture. In our study we had 3 cases of bleeding and two cases of access haematoma. None of these cases needed neither blood transfusion nor re-intervention.

It is important to highlight that the study used different doses of rt-PA. Likewise most of the previous studies, Sofocleous et al didn't comment on the duration between the thrombosis and performing the procedure.

Forty patients were randomized prospectively in Vogel et al,[20] study to undergo pulse spray thrombolysis with use of rt-PA 4 mg in 4 mL of normal saline solution, or mechanical thrombolysis with the Percutaneous Thrombectomy Device (PTD). The immediate anatomic success rate was 95%. The 3-month primary patency rates were 65% in both groups in comparison to our 65.63% primary patency six months post procedure.

Seven episodes of bleeding occurred in six patients given rt-PA; four were delayed 60–90 minutes after the procedure, one necessitated hospitalization, and two required additional therapies.

In his comparative study Vogel declared that the 4-mg dose of rt-PA is effective but results in more bleeding complications and longer hemostasis times than mechanical thrombolysis with use of the PTD.

A retrospective study was conducted in China and published in 2019 by Wang et al,[21] examined 30 cases of AVF thrombosis treated between January 2015 and January 2017. All patients received transcatheter thrombolysis performed at 2 to 72 h after diagnosis of AVF occlusion with angioplasty using a trans-brachial approach. A urokinase solution was injected for 15 to 20 min. Balloon dilatation was performed in all patients.

In this study patients were divided into two groups according to the site of stenosis. For type I stenosis (At or close to the anastomosis), primary patency was achieved in 62.5% of patients and secondary patency in 87.5% For type II stenosis (At the puncture site), primary patency was achieved in 92.9% of 14 patients while secondary patency was achieved all patients. After 6 months, the primary and secondary patency rates were 76.7% and 93.3%, respectively.

Two patients experienced bleeding at the puncture site during thrombolysis, which was stopped by compression with no serious bleeding. There were no cases with symptomatic pulmonary embolism. This is very similar to our rate of complications.

Choi reported that between March 2005 and October 2009 eighty-two patients with thrombosed AV grafts were treated with the Pharmacomechanical thrombolysis technique using 200,000 IU of urokinase dissolved in 5 mL of sterile normal saline and the solution was slowly infused over 5-minutes, AV graft surveillance to detect failing/failed access was followed by endovascular treatment.[22] They included patients with history of graft thrombosis less than 48 hours ago and who didn't have any endovascular salvage procedure for the thrombosed AVA in another institute. The technical and clinical success rates were 95% and 95%, respectively. The total number of thrombolysis sessions was 279. A post- intervention primary patency rate was 45% and 22% at 12 and 24 months, respectively. The secondary patency rate was 96% and 91% at 12 and 24 months, respectively. There were no major complications that required prolonged hospitalization • with surgical or medical treatment. There were no mortalities related to the procedure. These secondary patency results are very high for one and two years follow up following AVA salvage.

Despite our thorough literature research we didn't find exactly similar study to ours. For studies that have used rt-PA as a thrombolytic agent either the dose was variable or used only for AVG or a mechanical thrombectomy was done following thrombolysis.

As regards dose of rt-PA for thrombolysis of a recently thrombosed AVA there was no consensus. Time interval between thrombosis and intervention is crucial for the success of the trial to salvage the thrombosed AVA, but many studies didn't comment on this important factor.

Kuhan et al showed in their meta-analysis the lack of long-term data with little quality evidence to guide the management of thrombosed AVFs.[23]

Some studies tried to assess the longer patency rate following AVA salvage like Yilmazsoy and Ozyer in 2019.[24] Their subgroup analysis of AVG's demonstrated poor patency rates, with primary patency at 3-years of 0% and 5-year assisted primary and cumulative patency rates of 1% and 48%, respectively. In their study, AVF's had significantly better outcomes, with primary patency

of 45% at 3-years and assisted primary patency of 30% at 5-years.

Li et al study15 showed primary patency following AVG thrombolysis at 1,3 and 5 years was 43.2%, 20.2% and 7.7% respectively

We have many limitations of our study; the first is the small number of patients in each group and limited resources to treat our patients. Many patients were referred to us more than two weeks after the AVA thrombosis. These cases were not included in the study according to the study protocol but some of them had a trial to salvage the access and showed inferior results as regards immediate technical success and six months patency.

We need to follow up the patients for longer duration to re-assess the primary and assisted primary patency after one year and more.

Another difficulty we had was the compliance of the patients to have follow up visits. We had the information about the patency of the AVA sometimes by contacting the dialysis team where the patient had dialysis. We have advised the patients who had a successful procedure to have a bi-annual AVA duplex US scan but more than half of them didn't show up for the scan or mentioned they can't attend or they are not interested as long as the access is functioning well with no concern from dialysis team.

We believe according to our initial data that the technique of pulse rt-PA thrombolysis followed by AVA angioplasty is safe and effective in treating recently thrombosed AVA.

Using the higher dose -10mg- for rt-PA had a better primary and assisted primary patency after six weeks and six months. But these results were significantly better only in six months assisted primary patency. This higher success was not associated with higher incidence of bleeding or other complications.

Conclusions

Thrombolysis -using rt-PA- for a recently thrombosed AVA followed by angioplasty yields a high initial technical success rate either we use 6mg or 10mg of thrombolytic agent. However, six months primary assisted patency might suggest that the use of 10 mg carries a better outcome without an increase in the risk of bleeding.

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