A Prospective Randomized Study Comparing the Use of Paclitaxel-Coated PTA Balloon Catheters Versus Plain Balloon PTA Catheters to Treat Stenotic Segments at the Venous Anastomotic Site after Thrombectomy for Thrombosed Prosthetic Vascular Grafts for Dialysis

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ABSTRACT

Aim: *To compare the success rate, primary patency of thrombosed prosthetic vascular access grafts of the upper limb after thrombectomy and balloon dilatation of stenotic segments at venous anastomotic sites using either Paclitaxel-coated PTA balloon catheters or plain balloon PTA catheters.* ***Patients & methods:*** *Thirty seven (37) patients with thrombosed prosthetic vascular access PTFE grafts of the upper limb from October 2013 till February 2014, were randomized into two groups. After thrombectomy of the prosthetic graft, patients in group A underwent balloon dilatation of stenotic segment at venous anastomotic site using Paclitaxel-coated PTA balloon catheters, while in group B they were treated using plain balloon PTA catheters.* ***Results:*** *The success rate was 89.5% (n=17), 83.3%(n=15) in both groups respectively. The patency rate in 6 months was 82.4% for group A, while in group B it was 53.3%. After one year the patency rate was 58.8%. 33.3% for both groups respectively.* ***Conclusion:*** *Using Paclitaxel-coated PTA balloon catheters have higher patency rates in comparison to plain balloon catheters, but still these results are statistically insignificant may be due to small number of study sample.*
Key words: *Venous anastomosis stenosis, Paclitaxel-coated PTA balloon, graft thrombectomy.*

INTRODUCTION

Dialysis access failure caused by acute thrombosis is a common problem. In most scenarios of clotted arteriovenous (AV) grafts, a stenosis at the venous outlet of the graft would have precipitated the event by leading to diminished blood flow.[1] The National Kidney Foundation & Kidney Disease Outcomes Quality Initiative seeks to increase the use of autogenous fistulas, yet many patients continue to undergo hemodialysis with the use of prosthetic arteriovenous grafts.[2,3]

Prosthetic AV accesses tend to thrombose more frequently than autogenous accesses. Because the most common failure mode is neo-intimal hyperplasia at the venous anastomosis, they can usually be salvaged, providing long-term access without a significant disruption in a patient's dialysis schedule.[4]

Neo-intimal hyperplasia is much more prone to occur after vascular interventions such as vein bypass grafts, endarterectomies, arteriovenous fistulas, prosthetic bypass grafts, balloon angioplasty, endovascular stents and stent grafts. Although molecularly this process begins immediately after the vascular injury that accompanies the procedure, detectable intimal lesions classically form within a few weeks to 2 years.[5]

It is currently believed that neo-intimal hyperplasia starts as an acute inflammatory response. Because of the incomplete functional recovery of the repopulated endothelial cells and the phenotypic switch of smooth muscle cells, the acute inflammation often does not completely resolve, leaving behind a chronic inflammation in the intimal tissue. Inflammatory cells, particularly macrophages and T cells, are found in established intimal lesions.[6]

The use of systemic drug therapy to prevent the stenosis resulting from neo-intimal hyperplasia was first seriously investigated in the late 1970s. Various compounds were used but were poorly tolerated, have narrow therapeutic ranges, and have diminished efficacy when administered systemically.[7, 8]

These outcomes have led to the concept of local drug administration; where high doses of a therapeutic agent are administered directly to the desired part that to be treated of an artery or a vein without adverse systemic effects. The local

adminstration can result in drug concentrations in vascular tissues that are 400 to 1000 times higher than that achieved after systemic administration of the same compound.[9-12]

PATIENTS AND METHODS

This study was conducted over patients attending the vascular outpatient clinic at Ain Shams University hospitals. This was a prospective randomized study done upon 37 patients with chronic renal failure presenting with thrombosed prosthetic vascular access grafts (PTFE) of dialysis. The study sample presented to the outpatient clinic in the period from October 2013 till February 2014.

The inclusion criteria of these patients were:

1. Patients on regular haemodialysis having an AV graft (PTFE) for dialysis, from which they receive adequate dialysis sessions for the last 2 months.
2. The graft was recently thrombosed, for the first time from its creation.
3. Patient's approval to be included in the study.

The exclusion criteria were:

1. History of Upper limb DVT prior to AV access creation.
2. Previous thrombosis and thrombectomy of the AV graft.
3. Previous history of venous hypertension of the upper limb.
4. The presence of signs of infection of the prosthetic graft.
5. Patients having an AV graft for dialysis, from which they did not receive any adequate dialysis sessions.
6. Absence of brachial artery pulsations.

Every patient was subjected to:

1. History taking, putting in mind the last session the patient has had his dialysis through the graft
2. Clinical examination to exclude patients having signs of graft infection
3. Duplex Scanning to detect the presence of arterial insufficiency.

After that the patients were given numbers by random-number generator and divided into two groups:

- Group A: patients with odd numbers were treated by thrombectomy of the graft and balloon dilatation using Paclitaxel-coated PTA balloon catheter to the venous anastomotic site.
- Group B: patients with even numbers were treated by thrombectomy of the graft and balloon dilatation using plain balloons to the venous anastomotic site.

Procedure:

1. The procedure was done under local infiltration anesthesia; a skin incision was performed at the site of the PTFE graft in the mid arm while the patient was in the supine position.
2. Dissection and exposure of a good length of the graft (sufficient for application of vascular clamps) was done, then two vascular clamps were applied proximal and distal to the proposed incision site.
3. A transverse incision was made to the graft, a 4 F Fogarty's catheter was introduced towards the venous side for thrombectomy, then towards the arterial side for thrombectomy.
4. After ensuring of adequate thrombectomy, the incision in the graft was sutured with 5/0 prolene, before tying up the sutures, a 6 F (Prelude®, MeritMedical) sheath is introduced inbetween the sutre line.
5. Diagnostic angiogram was done from the graft to view the site of anastomosis, axillary vein up to the SVC.
6. A 0.035 J shaped guide wire (Terumo®, Terumo corporation) was manipulated to cross the lesion, this negotiation with the lesion was done by a combination of 4F or 5F diagnostic catheter (Performa®, MeritMedical).
7. For group (A) pre-dilatation of the anastomotic site was done with PTA balloon cathters over the wire 6-8 mm with different lengths according to the lesion then we apply a Paclitaxel-coated PTA balloon catheter (In.pact®, Admiral®) 6-8 mm with different lengths, while in group B only dilatation using plain PTA balloon cathters 6-8 mm in diameter with different lengths.
8. Completion angiography was done for evaluation of angioplasty results.
9. Technical success was considered when there is thrill over the graft.
10. If there was central venous stenosis or occlusion other than the venous anastomotic

site, it was corrected according to its site and degree.

11. Angiogram of the arterial anastomotic site was done to exclude anastomotic stenosis.
12. Removal of the sheath was done, with tying up the suture line, good hemostasis was ensured
13. Skin wound was closed with 3/0 prolene.
14. Patient was permitted to have dialysis from the graft the next day.
15. The procedure was followed up every 3 months, 6 months and one year using duplex ultrasound to detect the presence of restenosis at the venous anastomotic site.

RESULTS

This study was conducted on 37 patients with chronic renal failure presenting with thrombosed AV grafts (PTFE) of dialysis. The study sample presented to the outpatient clinic in the period from October 2013 till February 2014. In group A, 19 patients were included, while in group B, 18 patients were included.

The following table shows the demographic data of the studied sample, and showed no significant difference between both groups.

Table (1): Description of the studied patients

		Group A	*Group B*	*P value*
Age		42.94737 ± 8.49492	43.80056 ± 8.50665	0.798104
Gender	**Male**	8 (42%)	9 (50%)	Fisher's exact
	Female	11 (58%)	9 (50%)	
Side of the	**Right**	12	10	0.7431
AV graft	**Left**	7	8	Fisher's exact

The following table shows patients' co-morbid factors, and there is no significant difference between booth groups.

Table (2): Co-morbid factors of both studied groups

		Group A	*Group B*	*P value*
Diabetes mellitus	Yes	14	12	0.7281
	No	5	6	Fisher's exact
Hypertension	Yes	13	13	1.0000
	No	6	5	Fisher's exact

All patients were subjected to thrombectomy of the graft followed by diagnostic angiogram to determine the site of the lesion and if there were other central lesions or not.

The following table shows the sites of stenotic segments shown during diagnostic angiogram

Table (3): Description of the location of the lesion in the studied group.

		Group A	*Group B*	*P value*
Venous anstomotic side of	Yes	19	18	1.0000
the graft	No	0	0	Fisher's exact
Other central sites	Yes	1	0	1.0000
	No	18	18	Fisher's exact

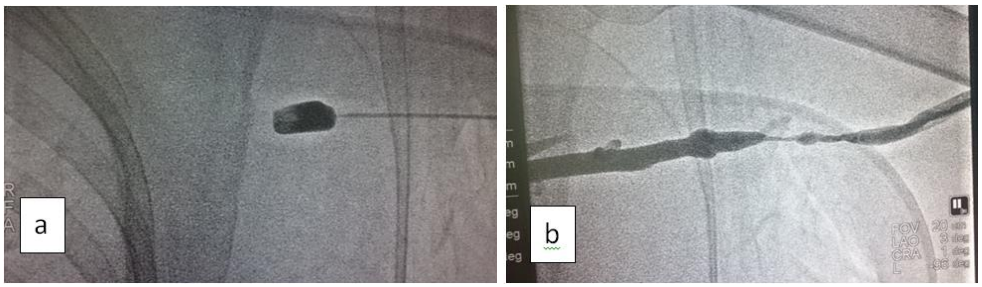

Fig. (1): A patient with graft thrombosis. (a) During thrombectomy using a Fogarty's catheter. (b) Diagnostic angiogram after thrombectomy showing stenosis at venous anastomotic site

After the diagnostic angiogram, balloon dilatation of the venous anastomotic site was done, in group A we used Paclitaxel-coated PTA balloon catheters, while in group B we used plain PTA balloon catheters.

A successful intervention was defined as having a thrill over the graft, and the patient was able to have a complete dialysis session from it the next day. The following table showed these results.

Table (4): Successful intervention in both groups

		Group A	*Group B*	*P value*
Successful intervention	Yes	17(89.5%)	15(83.3%)	0.6599
	No	2(10.5%)	3(16.7%)	Fisher's exact

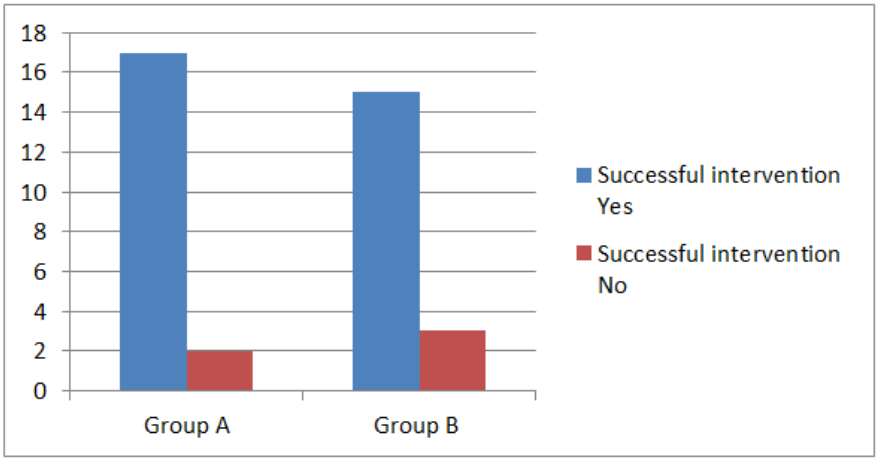

Fig. (2): Successful intervention in both groups.

All of these patients were followed up for 3, 6, 12 months, considering the graft was patent if it had a thrill over it and the patient was having efficient dialysis from this AV graft.

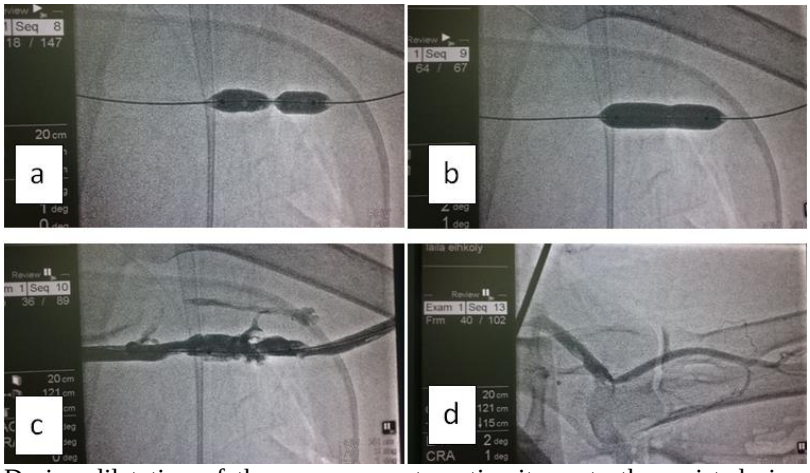

Fig. (3): (a,b): During dilatation of the venous anastomotic site, note the waist during dilation and its disappearance after complete dilation. (c): The venous anastomotic site after dilation (d) diagnostic angiogram to the arterial anastomotic site

For the patent AV grafts from which the patient has had dialysis and was having a thrill over it, duplex ultrasound was done to detect the presence of restonosis at the venous anastmotic site.

The following table showed these results.

Table (5): Patency rates at 3,6,12 months.

		Group A	*Group B*	*P value*
Patency at 3 months	Yes	17(100%)	12(80%)	0.0917
	No	0	2	Fishe r's exact
Restenosis	Yes	0	1	
Patency at 6 months	Yes	14(82.4%)	8(53.3%)	0.3544
	No	2	4	Fisher's exact
Restenosis	Yes	1	0	
Patency at 12 months	Yes	10(58.8%)	5(33.3%)	> 0.9999
	No	3	2	Fisher's exact
Restenosis	yes	1	1	

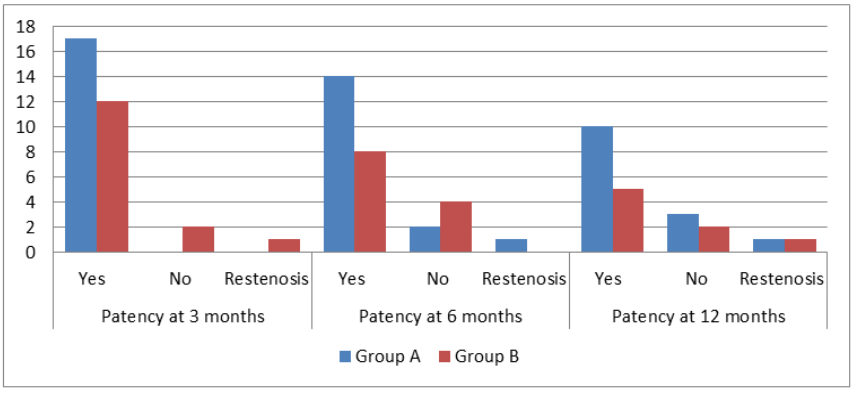

Fig. (4): Patency rates at 3,6,12 months.

Inspite of the higher patency rate in group A, yet the P value of both groups showed a non significant result.

DISCUSSION

In our study, 37 patients were diagnosed of having thrombosed AV grafts, were treated by mechanical thrombectomy and balloon dilation of the venous anastomotic site, 32 patients were able to have dialysis from their access the next day.

Of those 32 patients, 17 patients had their venous anstomotic site treated by Paclitaxel-coated PTA balloon catheters while the other 15 were treated using plain PTA balloon catheters.

The hypothesis behind using Paclitaxel-coated PTA balloon catheters was that the most common failure mode of prosthetic grafts for dialysis is intimal hyperplasia at the venous anastomosis,[4] so using it will give us better patency rates.

Using Paclitaxel-coated PTA balloon catheters gave us a patency rate of 100%, 82.4%, 58.8% for 3, 6, 12 months respectively, in comparison to 80%, 53.3%, 33.3% for 3, 6, 12 months respectively in the other group in which we used ordinary balloons. It was obvious that using drug coated PTA balloons gave us a high patency rate than plain balloons.

The surgical option for treatment of venous anastomotic site stenosis was patch angioplasty. In a prospective study comparing the surgical option with the endovascular option for treating venous anastomotic site stenosis after graft thrombectomy, it was found that, in 83% of the surgical group and in 72% of the endovascular group, graft function was immediately restored, The postoperative graft function rate was significantly better in the surgical group ($p< 0.05$). Thirty-six percent of grafts managed surgically remained functional at 6 months and 25% at 12 months. In the endovascular group, 11% were functional at 6 months and 9% by 12 months.[13]

In the study by Kohler et al. over a sheep model, they used a bioabsorbable vascular wrap paclitaxel-eluting mesh, the mesh was placed around the distal end of the graft and venous anastomosis. 8 weeks after implantation, the grafts and veins were harvested for histologic examination. After histologic processing neointimal area was significantly reduced in the paclitaxel mesh groups.[14]

In another study conducted over 34 patients trying to salvage an AV access graft by applying self expandable nitinol stents to the venous anastomotic side, it was found that 88% of grafts were functioning at 6 months' follow-up, and 63% of the entire group had survived without the need for additional procedures. Among those with the need for repeat interventions, 81% had new lesions outside of the stent, and 57% had new lesions within the stent. In 38% of cases, new stenoses were located both outside and within the stent.[15]

Clinical trials with antiplatelet agents have failed to provide significant improvement in patency. Saratin (an inhibitor of the vWF-dependent binding of platelet to collagen interaction), which inhibits platelet adhesion to the injured vascular wall, has shown promise in a canine model of dialysis access failure but has not yet been tested in a clinical setting.[16]

In a prospective, multicenter trial, randomly assigning 190 patients who were undergoing hemodialysis and who had a venous anastomotic stenosis they underwent balloon angioplasty alone or balloon angioplasty plus placement of a stent graft. The 6 months patency rate of the treatment area was significantly greater in the stent-graft group than in the balloon-angioplasty group (51% vs. 23%, $P<0.001$).[17]

Using noncompliant high-pressure balloons in a cohort of 13 patients to assist surgical thrombectomy for thrombosed hemodialysis grafts gave a success rate of 100%, and a primary patency rate of 77% at 1 month, 62% at 3 months, and 38% at 6 months.[18]

A lot of options have been used for the salvage of a thrombosed graft in order to treat the intimal hyperplasia that causes stenosis at the venous anastomotic site, a surgical option with patch angioplasty, balloon dilatation, application of a self expandable stent, application of a stent graft. We used drug coated balloons, and it appears to be promising as regard the patency rate.

CONCLUSION

Thrombosis of arteriovenous (AV) grafts caused by stenosis at the venous anastomosis is a well-described problem. Inspite the recommendations for creating autogenous

vascular access, yet we cannot exclude the use of prosthetic vascular grafts in patients having regular dialysis sessions.

Our study showed that using Paclitaxel-coated PTA balloon catheters have higher patency rates in comparison to plain balloon catheters, but still these results are insignificant , may be due to a small sample number. Larger samples may be needed to verify these results.

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