British Journal of Medicine & Medical Research
8(12): 1053-1062, 2015, Article no.BJMMR.2015.537
ISSN: 2231-0614

SCIENCEDOMAIN *international*
www.sciencedomain.org

Lytic Infusion versus Bolus Therapy for Peripheral Arterial Thrombosis Management: The LIBRA Pilot Study

Jon C. George[1*] and Nemalan Selvaraj[1]

[1]Division of Interventional Cardiology and Endovascular Medicine, Deborah Heart and Lung Center, Browns Mills, New Jersey, USA.

Authors' contributions

This work was carried out in collaboration between both authors. Author JCG designed the study and finalized the draft of the manuscript. Author NS performed the data procurement and wrote the initial draft of the manuscript. Both authors read and approved the final manuscript.

Article Information

DOI: 10.9734/BJMMR/2015/18490
Editor(s):
(1) Vijay K Sharma, Division of Neurology, Yong Loo Lin School of Medicine, National University of Singapore, National University Hospital, Singapore.
(2) Chan Shen, Department of Biostatistics, MD Anderson Cancer Center, University of Texas, USA.
Reviewers:
(1) Lewis S. Coleman, Tulare Regional Medical Center, Visalia, California, USA.
(2) Xing Li, Department of Health Sciences Research, Mayo Clinic College of Medicine, USA.
Complete Peer review History: http://www.sciencedomain.org/review-history.php?iid=1124&id=12&aid=9652

Short Research Article

Received 24th April 2015
Accepted 19th May 2015
Published 8th June 2015

ABSTRACT

Objective: To compare two intra-arterial catheter-directed thrombolysis (CDT) techniques (bolus vs infusion) with respect to clinical outcomes and resource utilization in the management of peripheral arterial thrombosis.
Methods: In a retrospective single-center study, 20 consecutive patients with acute or sub-acute thrombosis received tissue plasminogen activator (tPA) treatment administered either as a bolus via an irrigating balloon catheter (CDT-CLEARWAY group; n=10) or as a bolus followed by a continuous infusion using a traditional infusion catheter (CDT-INFUSION; n=10). Adjunctive therapies were administered at the discretion of the operator. Patients were followed for 30 days post-intervention for complications and major adverse clinical events.
Results: All 20 patients (12 men; median age 71) had Rutherford clinical stages 4-6 at presentation. Procedural success was achieved in all cases. The mean tPA amount required was reduced in the CDT-CLEARWAY group (8.9 mg vs 32.9 mg), as was the mean time to patency (2.2 hrs vs 16 hrs, P<.001). There were no bleeding complications in the CDT-CLEARWAY group while

**Corresponding author: Email: jcgeorgemd@gmail.com;*

one patient in the CDT-INFUSION developed intracranial and gastrointestinal hemorrhage. The CDT-CLEARWAY procedure was associated with a significant reduction in mean length of hospital stay (2.2 vs. 5.6 days, P<.001) and mean total cost, which were mostly due to the lack of ICU requirement for the CDT-CLEARWAY group. More patients in the CDT-CLEARWAY group (7/10 patients vs. 1/10 patients) underwent adjunctive thrombectomy procedures following disruption of the thrombus in the target vessel.

Conclusion: Significant reductions in total cost, amount of tPA used, and hospital stay were accomplished using a bolus dose of thrombolytic therapy through an irrigating balloon catheter versus a maintenance infusion dose through a standard infusion catheter, while maintaining the efficacy in restoring flow in target vessels.

Keywords: Peripheral arterial thrombosis; thrombolysis; catheter-directed; maintenance infusion.

1. INTRODUCTION

Although surgical embolectomy has been traditionally regarded as the established treatment for critical limb ischemia resulting from thrombotic peripheral arterial occlusive disease [1], intraarterial catheter-directed thrombolysis (CDT) has emerged as an effective alternative to surgery with few bleeding complications [2]. Various thrombolytic agents [3] and dose-related studies have since been performed to evaluate the optimal efficacy of CDT while reducing the bleeding risk: high-dose bolus [4], low-dose maintenance infusion [5], and pulse spray therapy [6]. However, the risk of prolonged infusion still portends modest morbidity and variable bleeding risks with hemorrhagic and ischemic stroke in 2.3% [7], intracranial bleeding in 2.1% [8], major hemorrhage in 5.1% [9], and minor hemorrhage in 14.8% [9] of patients undergoing CDT. Current consensus document on thrombolysis in the management of peripheral arterial occlusion [10] describes variable techniques for CDT without a preference for a single technique due to the lack of superiority data presently available. Additional studies are needed that compare various available modalities in order to guide clinicians' decisions.

Recently, an irrigating balloon catheter has been described as a safe and feasible technique for CDT [11]. The device utilizes a microporous PTFE low-pressure, noncompliant balloon to deliver thrombolytic drugs into the thrombus, potentially lowering the systemic concentration of the thrombolytic agent and lowering the risk of bleeding complications. We hypothesized that percutaneous delivery of directed bolus thrombolytic therapy using the irrigating balloon catheter would lead to at least equivalent clinical outcome compared to prolonged infusion therapy in the management of peripheral arterial thrombosis. We also hypothesized that the former method would lead to significant reduction of cost and length of hospital stay. We report here on a retrospective comparison of patients treated with each alternative at our center.

2. MATERIALS AND METHODS

2.1 Study Design

This was a retrospective single-center review of patient charts from 20 consecutive patients who presented to our institution between September 2011 and May 2013 with acute or sub-acute thrombotic occlusion of superficial femoral (SFA) and popliteal arteries or femoral-popliteal bypass grafts. This study was approved by the Institutional Review Board. Informed consent was not required because the data were to be analyzed retrospectively while maintaining the patients' anonymity. The patients were divided into 2 groups based on the thrombus treatment strategy: CDT with traditional infusion catheter with tissue plasminogen activator (tPA) bolus and maintenance infusion (CDT-INFUSION; n=10) (Fig. 1), or CDT using the irrigating balloon catheter with tPA bolus only (CDT-CLEARWAY; n=10) (Fig. 2).

2.2 Interventions

Treatment strategy to manage the acute thrombotic occlusion was at the discretion of the interventional operator and was based on the lesion type, anatomy, and morphology with variable adjunctive therapy modalities including thrombectomy, atherectomy, balloon percutaneous transluminal angioplasty (PTA), and stenting.

Complete angiography of the affected limb was performed via access of the contralateral femoral artery depending on the presumed thrombus location. A 6-French sheath was introduced into the affected limb and a guide-wire advanced through the thrombus into the distal vessel.

CDT-INFUSION: Patients who received CDT with traditional infusion catheter were treated with a 5-French Fountain infusion catheter (Merit Medical Systems, Inc., South Jordan, Utah) positioned across the thrombotic occlusion. The catheter utilizes an occluding wire to block off the end hole and direct the infusion therapy uniformly through the laser-drilled side holes. tPA was mixed as 10 mg per 50 mL normal saline and infused via the infusion catheter. A tPA bolus was first administered at a dose of 2-5 mg followed by a maintenance infusion dose of 0.5-1.0 mg/hr for 12-24 hours in the intensive care unit (ICU). Repeat angiography was performed at the end of the infusion period for vessel patency evaluation and for adjunctive treatment of any residual disease in the target vessel.

CDT-CLEARWAY: In the group who received CDT with irrigating balloon catheter, a 6-French ClearWay PTFE 5 x 50 mm balloon catheter (Atrium Medical Corporation, Hudson, NH, a business unit of MAQUET Cardiovascular) was positioned within the thrombotic occlusion. The tPA bolus was administered alone at a calculated dose of 0.2 mg per 1 cm of occlusion Following disruption of the thrombus in the target vessel, the operator had the option of performing mechanical thrombectomy for further thrombus burden reduction prior to any adjunctive treatment for residual disease in the target vessel.

In all patients, adjunctive treatment of the underlying lesions was left to the discretion of the operator and included PTA, stenting, and/or atherectomy.

During hospitalization, unfractionated heparin was used for anticoagulation to maintain activated partial thromboplastin time (aPTT) of 60-90 seconds and during the procedure to maintain activated clotting time (ACT) > 250 seconds. Post-procedure, acetylsalicylic acid and clopidogrel were recommended indefinitely.

2.3 Follow-up and Study Endpoints

Thrombolysis success was assessed by patency of the target vessel upon completion of the procedure. Patients were followed for recurrent thrombosis or re-intervention for the target limb for up to 30 days following the procedure. Any bleeding or vascular complications within 30 days of procedure were captured. Primary endpoints for the study were procedural outcomes measured by time to patency (time from diagnostic angiography to completion of revascularization), cost of therapy (procedural cost including equipment and hospital stay), and bleeding complications. Secondary endpoints included amount of lytic therapy administered, amount of contrast utilized for procedures, fluoroscopy time, and total procedure time.

2.4 Statistical Analyses

Descriptive statistics were used to present the mean ± standard deviation or median (range) for continuous variables and the counts (percentages) for categorical variables. Analysis of variance (ANOVA) was performed to determine statistical significance of comparative data.

3. RESULTS

3.1 Demographic and Disease Characteristics

A total of 20 patients (12 male, 8 female) with acute occlusions of previously stented SFA (n=14), de novo SFA (n=3) femoral artery bypass graft (n=2) or femoral-popliteal bypass graft (n=1) were included in the study; 10 patients treated according to the CDT-INFUSION protocol and 10 patients according to the CDT-CLEARWAY protocol. The 2 groups were well matched with respect to age, Rutherford clinical class (all class 4 or 6), and lesion location (Table 1). Patients in the CDT-CLEARWAY group had longer durations of complaint to clinical presentation (3.9 *vs.* 2.4 weeks, P=.01) with 10 patients reporting 4 week duration in the CDT-CLEARWAY group and 4 patients reporting 4 weeks and 3 patients reporting < 1 week in the CDT-INFUSION group). Lesion lengths also tended to be longer in the CDT-CLEARWAY group (4 lesions $\geq$ 50 cm, *vs.* no lesion $\geq$ 50 cm in the CDT-INFUSION group).

3.2 Procedures and Outcome

Positioning of the guidewire into the thrombus was successful in all cases. The amount of contrast utilized for procedures, the fluoroscopy time and the total duration of the procedure were similar between the 2 treatment groups (Table 2). The amount of tPA administered was significantly lower in the CDT-CLEARWAY group (8.9 mg versus 32.9 mg, *P*<.001). Adjunctive mechanical thrombectomy was performed in 7 of the patients in the CDT-CLEARWAY group and 1 patient in the CDT-INFUSION group following tPA administration. Successful thrombolysis was

achieved in all patients as ascertained by patency of target vessel following therapy, but the time to patency was significantly lower in the CDT-CLEARWAY group compared with the CDT-INFUSION group (2.2 hours versus 16 hours, *P*<.001).

Table 1. Patient demographic and clinical characteristics

		CDT-CLEARWAY n=10	**CDT-INFUSION n=10**
Age	Mean (SD)	71 (6)	72 (12)
	Range	63-81	46-90
Gender	Male, n (%) / Female, n (%)	3 (30) / 7 (70)	5 (50) / 5 (50)
Race	Caucasian, n (%) / African American, n (%)	9 (90) / 1 (10)	8 (80) / 2 (20)
History of smoking (past or present)		10	7
Concurrent medical illnesses			
Peripheral artery disease		10	10
Dyslipidemia		7	9
Hypertension		8	9
Coronary artery disease,		8	6
Diabetes,		3	5
Chronic kidney disease		3	3
Atrial fibrillation		0	3
Congestive heart failure		0	2
Cerebrovascular accident		0	1
Prestudy medications			
Aspirin		9	8
Beta-blocker		7	7
ACE inhibitor		4	8
Clopidogrel		6	6
Statin		6	5
Hypoglycemic agent		3	4
Diuretic		3	3
Nitrate		3	2
Prasugrel		3	1
Calcium channel blocker		0	3
Anticoagulant		1	2
Cilostazol		0	2
Angiotensin receptor blocker		0	1
Rutherford clinical stage			
Stage 4 - rest pain		7	7
Stage 6 - severe ischemic ulcers or gangrene		3	3
Type and location of occlusion			
SFA		9	8
In-stent		9	5
de novo		0	3
Femoral-femoral bypass graft		0	2
Femoral-popliteal bypass graft		1	0
Side - Left / Right		5 / 5	5 / 5
Duration of symptoms, number of patients			
1 day		0	1
4 days		0	2
2 weeks		0	2
3 weeks		1	1
4 weeks		9	4
Mean (SD) in weeks		3.9 (0.3)	2.4 (1.6) **
Length of occlusion (SD) in mm		401(192); 50, 650	278 (73); 200, 400

P<.01 by ANOVA comparing the 2 groups

Following successful thrombolysis, adjunctive procedures to address the underlying lesions were performed in all cases (Table 3) and included balloon angioplasty, atherectomy, and/ or stenting.

3.3 30-day Follow-up and Complications from Interventions

Thirty days after treatment, limb salvage was achieved in all patients. However, one patient in the CDT-INFUSION group developed intracranial hemorrhage and gastrointestinal bleeding while in the ICU, following the continuous infusion of tPA (29 mg of tPA in total). The patient required prolonged hospitalization and eventual transfer to higher level of care in another facility. Another patient stayed in the ICU for 7 days due to access site bleeding, sepsis, and respiratory failure requiring intubation. There were no other major complications during the 30-day follow-up period (classes C-E according to SIR Reporting Standards) [12,13], i.e., no major bleeding requiring transfusion, no amputation, no limb-threatening ischemia requiring surgery.

3.4 Resource Utilization

Due to the lack of ICU requirement for the CDT-CLEARWAY procedure, total hospital stay was significantly shorter in the CDT-CLEARWAY group compared with the CDT-INFUSION group (2.2 days *vs.* 5.6 days, P<.001) (Table 4). Costs were also significantly lower due primarily to ICU costs in the CDT-INFUSION group. The CDT-CLEARWAY group by contrast required additional equipment (e.g. rheolytic thrombectomy catheters) in order to further reduce the thrombus burden after disruption of the thrombus in the target vessel and prior to standard angioplasty and stenting.

Table 2. Intervention characteristics and 30-day outcome

	CDT-CLEARWAY n=10	CDT-INFUSION n=10
Procedure duration (minutes)		
Mean (SD)	131 (40)	165 (107)
Range	60, 191)	58, 386
Fluoroscopy duration (minutes)		
Mean (SD)	41 (19)	62 (66)
Range	14, 67	16, 240
Amount of contrast agent (mL)		
Mean (SD)	189 (80)	273 (106)
Range	90, 350	100, 435
tPA (mg)		
Mean (SD)	8.9 (7.8) ***	32.9 (7.9)
Range	2, 29	28, 53
Time to patency in hours, mean (SD)	2.2 (0.7) ***	16 (4)
Minimum	1.0	13.0
Maximum	1.5	26.1
Complications within 30 days		
GI bleed	0	1
CVA	0	1
Total (number of patients)	0	1

**** P<.001by ANOVA comparing the 2 groups*

Table 3. Adjunctive procedures

CDT-clearway group	n=10
Mechanical thrombectomy, balloon angioplasty, stent	6
Balloon angioplasty, stent	2
Balloon angioplasty	1
Mechanical thrombectomy, balloon angioplasty	1
CDT-infusion group	**n=10**
Balloon angioplasy	8
Atherectomy, balloon angioplasty	1
Atherectomy, mechanical thrombectomy, balloon angioplasty, stent	1

4. DISCUSSION

We compared an irrigating balloon catheter versus a standard infusion catheter for performance of thrombolysis along with adjunctive angioplasty and stenting in the treatment of lower extremity thrombosis in native or previously stented femoral or popliteal vessels and femoral-popliteal bypass grafts. Procedural success was achieved in all 20 cases. Mean time to patency was significantly reduced in the CDT-CLEARWAY compared with the CDT-INFUSION group (2.2 hrs *vs.* 16 hrs, respectively). There were no bleeding complications noted in the CDT-CLEARWAY group; in the CDT-INFUSION group, one patient developed intracranial hemorrhage and GI bleeding, requiring prolonged hospitalization and eventual transfer to higher level of care in another facility. This was consistent with the significant reduction of the mean tPA amount required in the CDT-CLEARWAY group when compared with the CDT-INFUSION group to achieve patency of the target vessel compared (8.9 mg *vs.* 32.9 mg).

Table 4. Length of hospital stay and hospital costs

	CTD-Clearway n=10	CTD-Infusion n=10	
Length of stay (days)			
Intensive Care Unit, mean (SD)	0 (0)	3.6 (3.0)	***
2 days		6	
3 days		2	
7 days		1	
11 days		1	
Hospital (non-ICU), mean (SD) min, max	2.2 (1.5) 1, 6	2.0 (2.0) 0, 6	
Total, mean (SD) min, max	2.2 (1.5) 1, 3	5.6 (2.6) 3, 11	**
COSTS			
Intensive Care Unit	0 (0)	12,960 (10,893)	***
Hospital (non-ICU)	5,280 (3,542)	4,800 (4,800)	
Equipment	5,813 (1,269)	3,828 (3,640)	
Total	11,093 (3,995)	21,588 (10,561)	**

*** P<.01and *** P<.001 by ANOVA comparing the 2 groups*

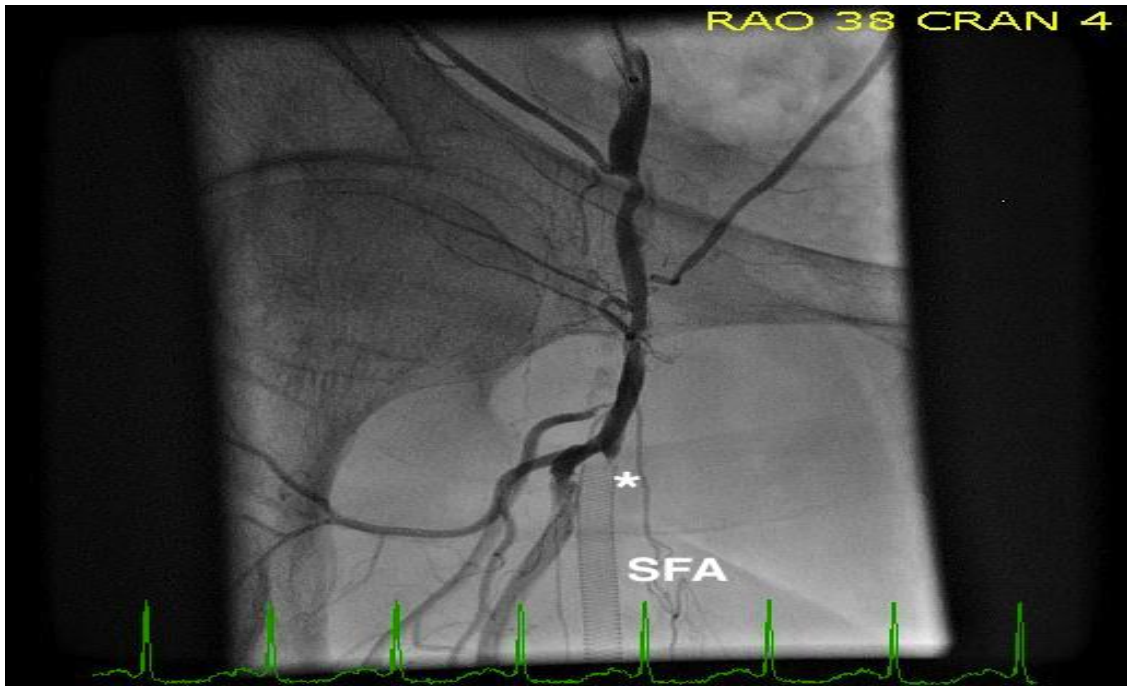

Fig. 1a

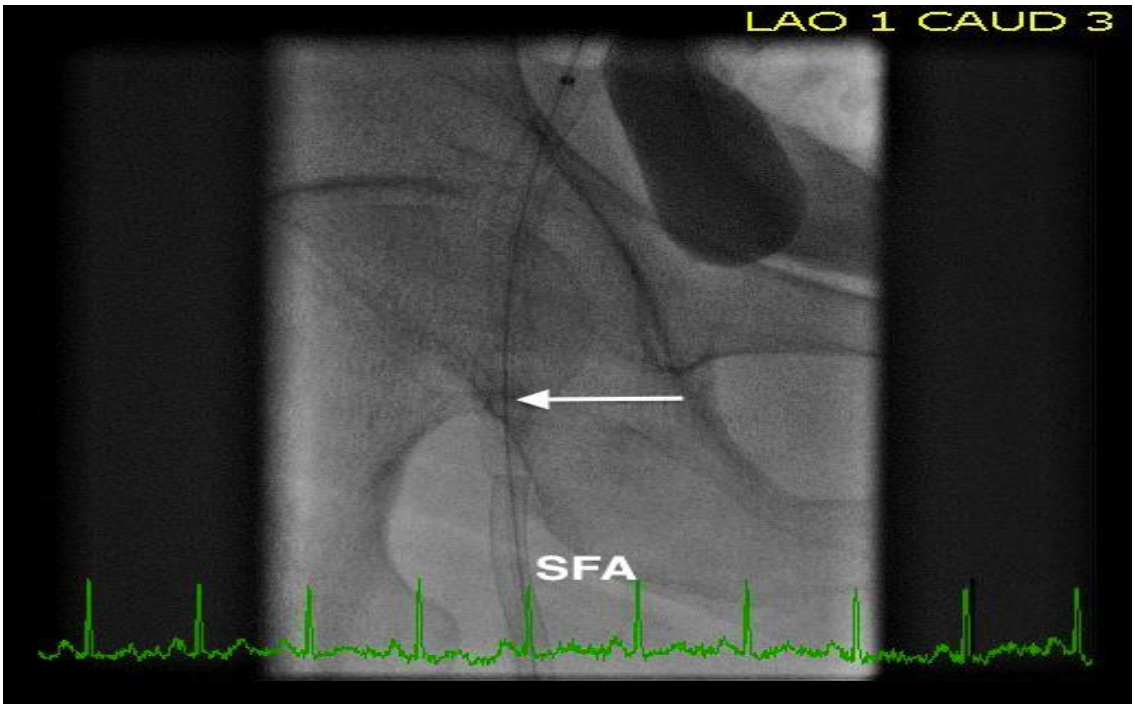

Fig. 1b

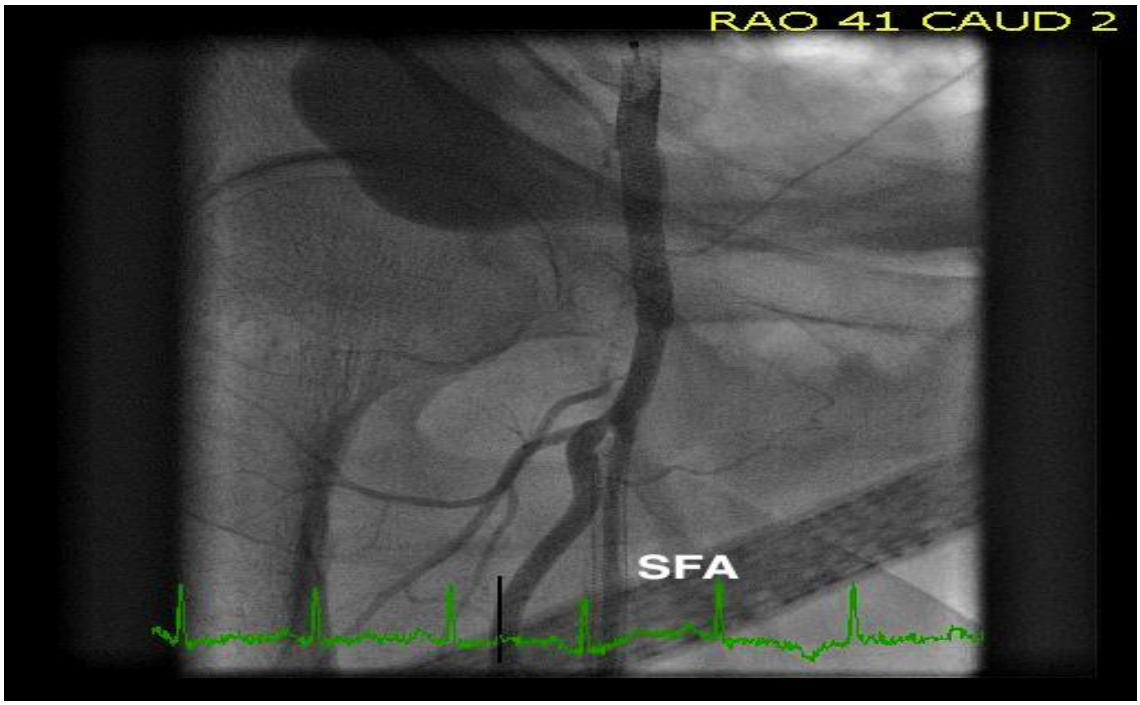

Fig. 1c

Fig. 1. Angiography demonstrating acute thrombosis (*) in a previously stented SFA [1a], treated with thrombolysis using a standard infusion catheter (arrow) [1b], and excellent angiographic result following treatment [1c]

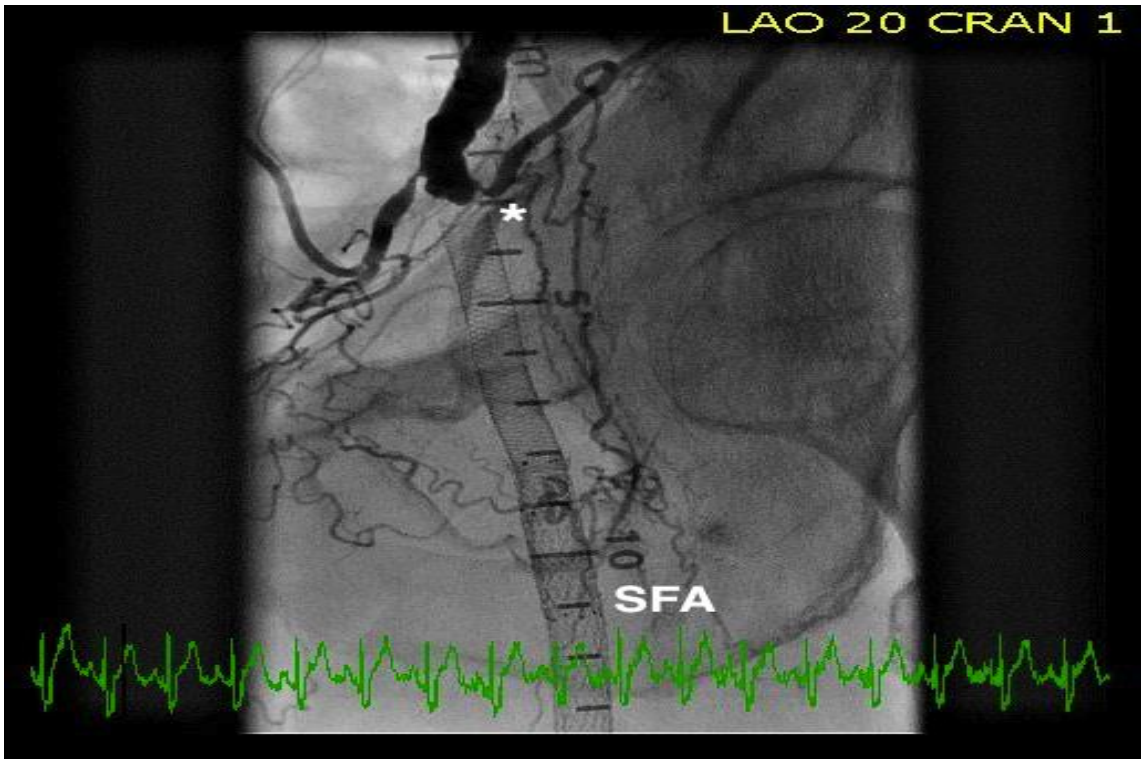

Fig. 2a

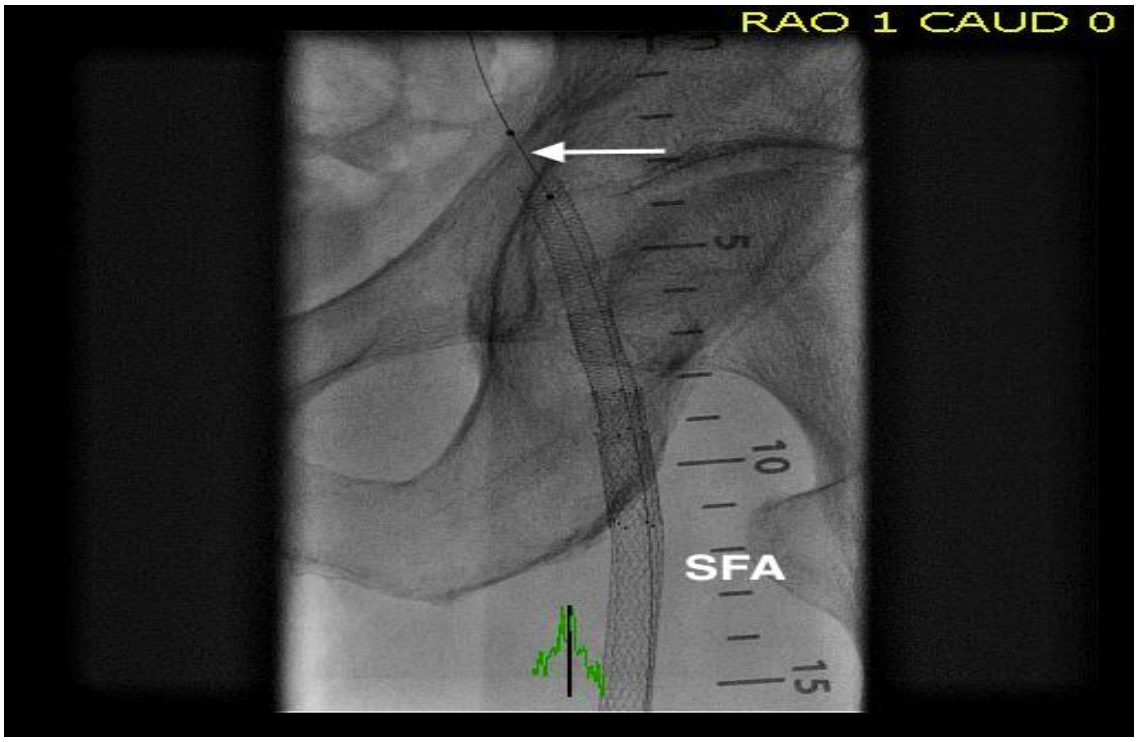

Fig. 2b

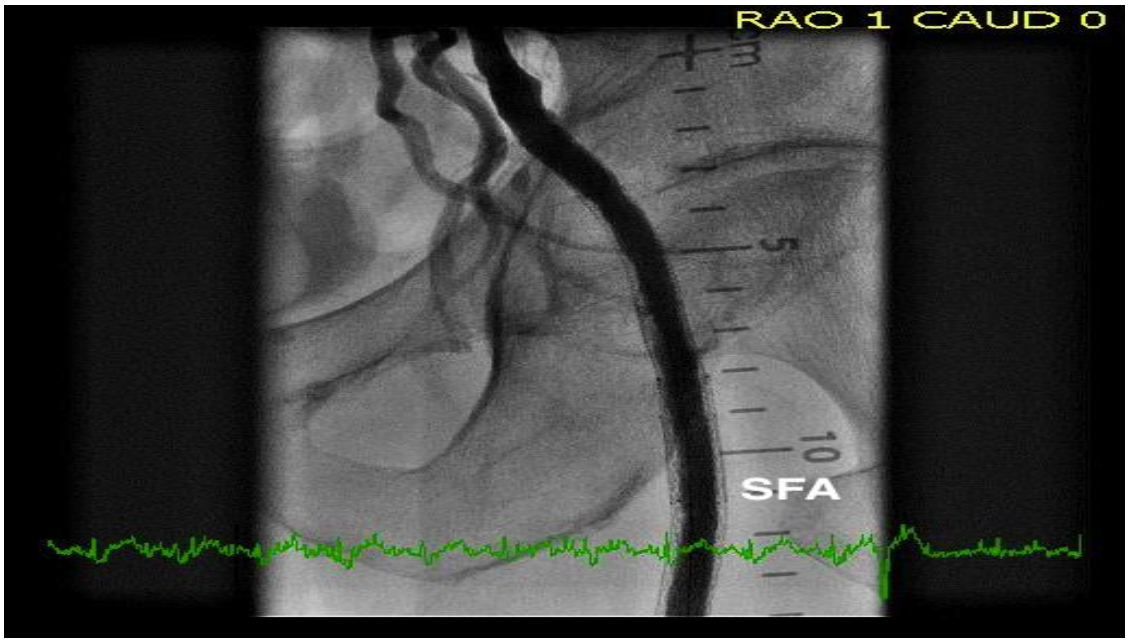

Fig. 2c

Fig. 2. Angiography demonstrating acute thrombosis (*) in a previously stented SFA [2a], treated with thrombolysis using an irrigating balloon catheter (arrow) [2b], and excellent angiographic result following treatment [2c]

Use of the irrigating balloon catheter was associated with a significant reduction in average length of hospital stay and average total cost, mostly due to the lack of ICU requirement compared to standard infusion catheter. Although average procedure time and average contrast dose utilized per case were not significantly different between the 2 groups of patients, there was a notable technical difference due to the need to perform repeat angiography at the end of the standard infusion procedure to evaluate vessel patency after thrombolytic administration and to perform additional angioplasty and stenting for any residual disease in the target vessel. Another technical difference was that patients in the CDT-CLEARWAY group had an increased number of thrombus burden reduction procedures following disruption of thrombus in the target, thus requiring additional thrombectomy equipment in order to further reduce thrombus burden prior to standard angioplasty and stenting.

Generalization of this study's findings is limited by the small size of the study and the single-center setting. The study is further limited by the non-random inclusion of patients into each treatment group, which may have affected the outcome.

5. CONCLUSION

In summary, thrombolytic administration with the irrigating balloon catheter in the setting of acute thrombotic disease of previously stented femoral or popliteal arteries or femoral-popliteal bypass graft is equally as efficacious in restoring flow as the traditional infusion method, with adjunctive angioplasty and stenting. Our study demonstrated that significant reduction in amount of tPA per procedure, average hospital stay and average total cost of treatment was accomplished with thrombolytic therapy with the irrigating balloon catheter compared to treatment with a standard infusion catheter.

ETHICAL APPROVAL

This study was approved by the Institutional Review Board. Informed consent was not required since the data were analyzed retrospectively while maintaining patient anonymity.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

REFERENCES

1. Ouriel K. Surgery versus thrombolytic therapy in the management of peripheral arterial occlusions. J Vasc Interv Radiol. 1995;6:48-58.
2. STILE Investigators. Results of a prospective randomized trial evaluating surgery versus thrombolysis for ischemia of the lower extremity. The STILE Trial. Ann Surg. 1994;220(3):251-68.
3. Robertson I, Kessel DO, Berridge DC. Fibrinolytic agents for peripheral arterial occlusion. Cochrane Database Syst Rev. 2010;3: CD001099.
4. Braithwaite BD, Buckenham TM, Galland RB, et al. Prospective randomized trial of high-dose bolus versus low-dose tissue plasminogen activator infusion in the management of acute limb ischaemia. Br J Surg. 1997;84:646-50.
5. Sebastian AJ, Robinson GJ, Dyet JF, et al. Long-term outcomes of low-dose catheter-directed thrombolytic therapy: A 5-year single-center experience. J Vasc Interv Radiol. 2010;21:1004-10.
6. Yusuf SW, Whitaker SC, Gregson RHS, et al. Immediate and early follow-up results of pulse spray thrombolysis in patients with peripheral ischaemia. Br J Surg. 1995;82: 338-40.
7. Dawson K, Armon A, Brauthwaile B, et al. Stroke during intra-arterial thrombolysis: A survey of experience in the UK. Br J Surg. 1996;83:568.
8. Ouriel K, Veith FJ, Sasahara AA, et al. Thrombolysis or peripheral arterial surgery (TOPAS): Phase I results. J Vasc Surg. 1996;23:64-75.
9. Berridge DC, Niakin GS, Hopkinson BR. Local low-dose intra-arterial thrombolytic therapy, the risk of major stroke and haemorrhage. Br J Surg. 1989;76:1230-2.
10. Working Party on Thrombolysis in the Management of Limb Ischemia. Thrombolysis in the management of lower limb peripheral arterial occlusion—a consensus document. J Vasc Interv Radiol. 2003;7:337-49.
11. Shammas NW, Weissman NJ, Coiner D, et al. Dethrombosis of lower extremity thrombus by local delivery of thrombolysis using Clearway transcatheter balloon irrigation: A feasibility study. Cardiovasc Revasc Med. 2011;12:350-4.
12. Sacks D, McClenny TE, Cardella JF, Lewis CA. Society of Interventional Radiology Clinical Practice Guidelines. J Vasc Interv Radiol. 2003;14:199-202.
13. Patel N, Sacks D, Patel RI, et al. SIR Reporting Standards for the Treatment of Acute Limb Ischemia with Use of Transluminal Removal of Arterial Thrombus. J Vasc Interv Radiol. 2003;14: 453-465.

Peer-review history:
The peer review history for this paper can be accessed here:
http://www.sciencedomain.org/review-history.php?iid=1124&id=12&aid=9652