Midterm results of catheter-directed thrombolysis in patients with vasculitis with acute ischemia

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Received: 16 February 2023
Revised: 22 February 2023
Accepted: 26 February 2023
Published: 9 June 2023

The Egyptian Journal of Surgery 2023, 42:280–285

Background
Acute limb ischemia (ALI) of the lower extremities remains and will always be a challenging dilemma with a high risk for major amputation. Treatment of ALI has shifted toward endovascular therapies. This study aimed to assess the outcomes of lytic therapy in patients with vasculitis patients with acute ischemia.
Patients and methods
This prospective study included patients with vasculitis with ALI of the upper and lower extremities treated via endovascular intra-arterial thrombolysis between January 2016 and December 2019. A total of 69 patients underwent intra-arterial thrombolysis via alteplase. A 24- and 48-h follow-up angiogram was done to monitor the results. Complications, need for secondary intervention, and limb survival without amputation were assessed for 2–3 years of follow-up.
Results
Complete clot lysis was seen in 60 of 69 patients, with complete resolution of pain and cyanosis. Access-site hematoma and one pseudoaneurysm were treated with manual compression under echo guidance. Three cases experienced ischemic pain for two weeks after intervention. Six patients in the study did major amputation owing to sudden discontinuation of lytic therapy before complete thrombolysis.
Conclusions
Endovascular thrombolysis remains an effective treatment option for patients with vasculitis presenting with ALI.

Keywords:
acute limb ischemia, thrombolysis, vasculitis

Egyptian J Surgery 42:280–285

1110-1121

Introduction

Acute limb ischemia (ALI) is a condition that occurs secondary to an abrupt decrease in the blood flow to a limb. Consequently, this poses a real threat to the viability of the limb and the patient's survival. Hence, proper evaluation and intervention should be carefully planned. Symptoms include pain, coldness, numbness, color changes, a sudden increase in ischemic symptoms in patients with a history of peripheral arterial disease, and loss of sensation and/or motor power. It necessitates a period of 14 days or less to be classified as 'acute' limb ischemic presentation [1].

Common causes of ALI include embolism, thrombosis, arterial aneurysm, dissection, and traumatic injuries. Other less frequent etiologies involve vasculitis, adventitial cystic disease, popliteal entrapment syndrome, thrombophilia, and foreign body embolization (as is the case with intra-arterial drug addicts) [2]. Vasculitis is simply an inflammation of the arteries. It usually comes in bilateral affection and associated systemic manifestations, for example, fever. In addition, signs of connective tissue disease are often encountered. Vasculitis constitutes a huge number of disorders that affect different arterial sizes and sites. Its involvement could extend from chronic limb ischemia to ALI and loss [3].

According to Rutherford, ALI has been classified into three stages: viable, threatened, and irreversible. These are labeled as classes 1, 2, and 3, respectively. However, class 2 can be expanded according to the degree of motor loss into 2a and 2b, with the latter having early signs of motor affection [4].

Until the 1990s, the treatment of acute arterial ischemia of the lower leg consisted primarily of surgery, embolectomy, reconstruction, and/or amputation. Gradually fibrinolysis took over, and after the introduction of the human plasminogen activator (rt-PA), the algorithm of treatment at most

places has been a catheter-directed infusion of rt-PA immediately following primary angiography. Actilyse is a human plasminogen activator that clears the cross-linked fibrin mesh of the clot. Its infusion into the clot facilitates the lytic process. During the same procedure, the patient can also have percutaneous transluminal angioplasty; many are stented and/or undergo vascular surgery [5].

In our study, we focus on the use of rt-PA in patients with vasculitis with acute ischemia and discuss its favorable results, complications, need for secondary intervention, and limb survival without amputation for 2–3 years of follow-up.

Patients and methods

This was a prospective interventional study with an analytic component conducted in Mansoura University Hospital and Mansoura Emergency Hospital with a catchment area of 15 million population from January 2016 to December 2019. The institutional committee granted ethical approval. All patients were adults who gave written consent. Vasculitic patients with ALI (class 1 and 2a according to Rutherford classification) lasting less than 14 days were included in the study [6]. In contrast, classes 2b and 3 were excluded from our inclusion group. Patients with evidence of atherosclerosis (diabetics) and patients with absolute contraindication to thrombolytic therapy were excluded from the study. We excluded patients who lost follow-up at the end of the study and patients who refused to provide consent.

During the study period, we examined more than 200 patients; only 69 patients met the inclusion criteria and were committed to our follow-up protocol. All patients filled out a visual analog scale sheet to assess preoperative pain score. Pictures of limb cyanosis and tissue loss were kept for postoperative comparison. Clinical presentation was nearly identical, including signs of severe ischemia in all cases and gangrene of the forefoot and the toe. According to immunologist recommendations, all patients received immunosuppressive therapy before and after the intervention.

Technical success: technical success was defined on the basis of angiography performed directly after the procedure as restoration of antegrade flow and reduction of thrombus burden by more than 95% by volume.

Clinical success: clinical success was defined as technical success and relief of acute ischemic symptoms at 30 days.

Overall clinical success: overall clinical success was defined as relief of acute ischemic symptoms and the patient's return to at least his/her preocclusive clinical baseline level after thrombolysis and adjunctive procedures.

Technique

The surgical procedures were carried out under local anesthesia. A 6-F sheath was placed in an antegrade fashion in the common femoral artery of the affected side, through which a 4-F Berenstein catheter was introduced for selective angiography of the ischemic limb. Then, the 20-cm or 50-cm-long infusion 4-F Fountain Infusion catheter (Merit Medical, 1600 West Merit Parkway, South Jordan UT 84095 USA) was inserted into the occluded vessel and a loading dose of Actilyse according to body weight (8 ml average) was administered employing a pulse-spray technique for 1 mg/min into the fountain catheter in the operative room and then 1 ml/h in the ICU (the most frequently used regimen was 1 mg/h or 0.05 mg/kg/h) [7].

Cross-over sheath and 5-F Fountain catheter were introduced from the healthy limb to cover the occluded contralateral iliac and common femoral artery.

In the ischemic upper limbs, a 6-F sheath was placed in the axillary or proximal part of the brachial artery guided by dynamic ultrasound. A low dose of unfractionated heparin (500 IU/h) was introduced through the sheath by a syringe pump with monitoring of the blood count and coagulation profile in the ICU [8].

Follow-up angiogram was done 24 and 48 h after starting the Actilyse to monitor the effect on the target vessel. If there was no response on the first angiogram (after 24 h of continuous regular Actilyse infusion), the whole procedure was stopped, and another technique for revascularization was performed. During the second follow-up angiogram, if the infusion area of the catheter did not cover an occluded segment in the artery, repositioning the catheter was done to cover the occluded segment, and Actilyse was continued for another 24 h. Percutaneous transluminal angioplasty or stenting was performed after thrombolysis, if necessary. Mechanical thrombectomy devices were not used.

During hospitalization, low-molecular-weight heparin (Clexane, Sanofi-Aventis, Paris, France) was used. Then, oral acetylsalicylic acid and clopidogrel in a dose of 75 mg/24 h were recommended in all

patients for 6 months, in addition to the immunosuppressive therapy prescribed by the immunity physician. All patients were re-evaluated 2 weeks after the procedure, then after 1, 3, 6, 9, and 12 months, then yearly by clinical examination, hand-held Doppler, and ultrasound duplex examination. If any sign of vessel occlusion or stenosis was detected on the follow-up, a new plan for revascularization was implemented.

During the scheduled follow-up period, we assessed complications, need for secondary intervention, and limb survival without amputation.

A good outcome in this study represented limb revascularization and salvage. Meanwhile, failure of limb revascularization and subsequent major amputation represented poor outcome.

Minor amputation was defined as amputation at level of ankle joint and below (as forefoot and toes amputation). Meanwhile major amputation represented amputation above ankle joint (as below and above the knee amputation).

Statistical analysis

Data were analyzed using the Statistical Package for the Social Sciences (SPSS) program for Windows (Standard version 21). The normality of data was first tested with the one-sample Kolmogorov–Smirnov test. Qualitative data were described using numbers and percentages. Association between categorical variables was tested using the χ^2 test. Continuous variables were presented as mean±SD for normally distributed data.

Significant variables entered into regression model using forward Wald statistical technique to predict the most significant determinants and to control for possible interactions and confounding effects. Kaplan–Meier test was used for survival analysis, and the statistical significance of differences among curves was determined by the Log-rank test.

For all aforementioned statistical tests done, the threshold of significance was fixed at a 5% level. The results were considered significant when P value less than or equal to 0.05. The smaller the P value obtained, the more significant the results.

Results

Patient enrollment in this study started in January 2016 and ended in December 2019, and follow-up continued till December 2020. A total of 69 patients with acute ischemia were included (27 males and 42 females) to investigate the outcome of lytic therapy. The age ranged between 35 and 68 years. Overall, 27 patients had systemic lupus erythematosus, 21 patients experienced thromboangiitis obliterans, six patients had polyarteritis nodosa, and 15 patients had rheumatoid arthritis.

A total of 18 (26.08%) patients in our study had upper limb ischemia, two cases had occluded axillary artery, seven cases had occlusion at brachial artery bifurcation. In contrast, the other nine cases were occluded distal to the brachial bifurcation.

Moreover, 51 (73.91%) patients experienced lower limb ischemia. Their initial site of occlusion was variable: two cases had iliac occlusion, five cases had isolated occlusion at superficial artery occlusion, 12 cases had at the level of both superficial artery occlusion and tibials, whereas 32 cases at the level of tibials. Patient demographics are shown in Table 1.

Patients enrolled in the study presented with acute ischemic manifestations due to vessel occlusion by thrombus within 2 weeks. After completion of the alteplase therapy, follow-up angiography after 48 h showed successful and complete clot lysis in 54 (78.26%) patients with complete resolution of pain and cyanosis (Figs 1 and 2).

Six (8.69%) patients required another 24 h of alteplase to give the desired result (complete patency of vessels).

Table 1 Patient characteristics among the studied group

Patient characteristics	The study groups (*N*=69)
Age (years)	
Mean±SD	52.33±9.52
Minimum–maximum	35–68
≤50 years	29 (42.0)
>50 years	40 (58.0)
Sex	
Male	27 (39.1)
Female	42 (60.9)
Etiology	
SLE	27 (39.1)
TAO	21 (30.4)
Rheumatoid	15 (21.7)
PAN	6 (8.7)
Limb	
Upper	19 (27.5)
Lower	50 (72.5)
Cyanosis	6 (8.7)
Pain	9 (13.0)

PAN, polyarteritis nodosa; SLE, systemic lupus erythematosus; TAO, thromboangiitis obliterans.

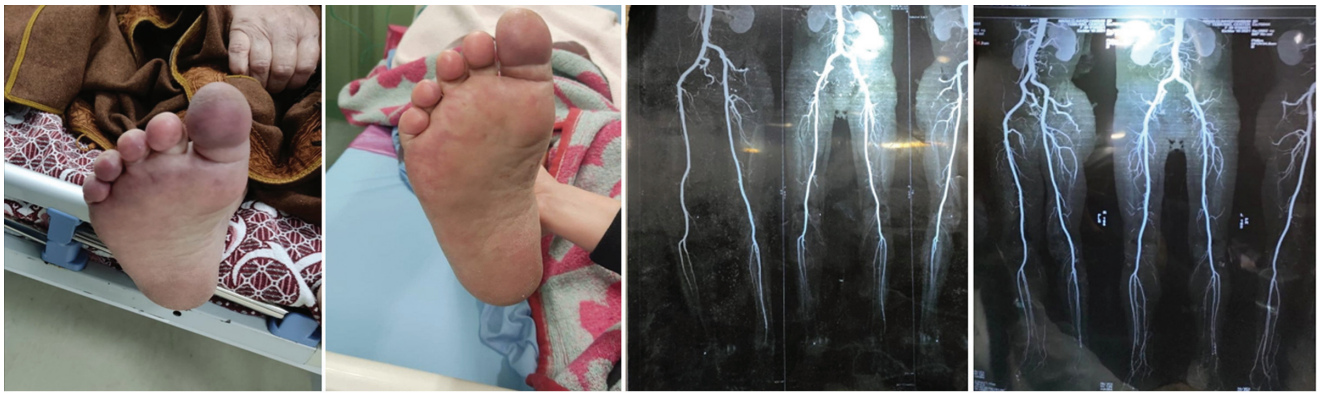
Meanwhile, three (4.35%) patients had incomplete lysis despite 72 h of continued alteplase infusion. Their angiogram revealed patency of the popliteal and one tibial artery, compared with none before lysis (the three patients' limbs showed resolution of cyanosis but the pain did not resolve completely until after 2 weeks of follow-up).

Six (8.69%) patients showed massive orifice bleeding, decrease in fibrinogen level derangement of bleeding profile, and the lytic therapy was interrupted. Despite trial surgical thrombectomy, their limbs showed deep cyanosis and intolerable pain, so major limb amputation was implemented. A total of 12 patients underwent minor amputation 4-weeks after revascularization. The relation between outcome and patient characteristics is shown in Tables 2 and 3. Complications included access-site hematoma in one lower limb and one pseudoaneurysm in lower limb treated with manual compression under ultrasound guidance [9].

Table 2 Results

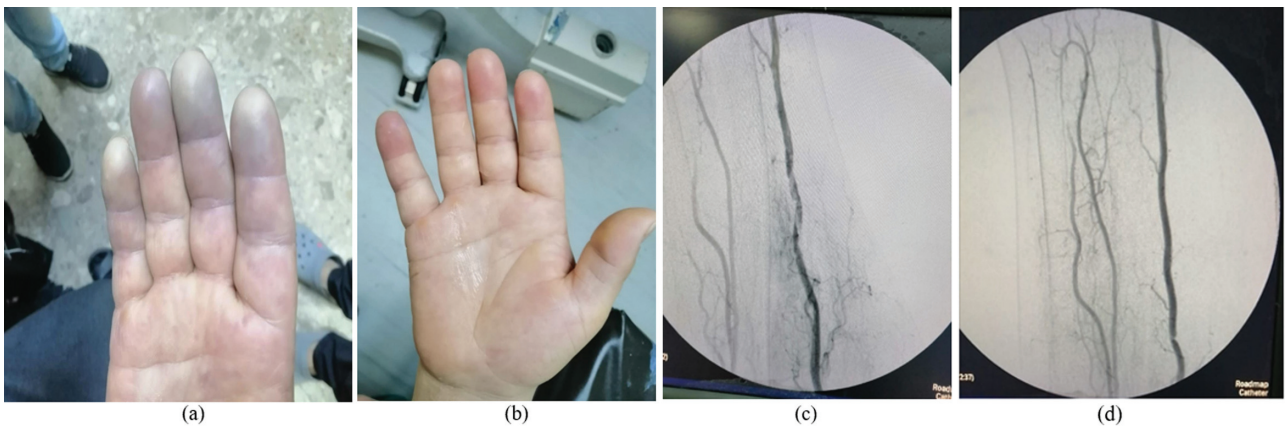
Patient characteristics	The study groups (*N*=69)
Amputation	
Minor amputation	12 (17.4)
Major amputation	6 (8.7)
Survival	
Died	3 (4.3)
Survived	66 (95.7)
Outcome	
Good	49 (71.0)
Poor	20 (29.0)
Results of lytic therapy	
Successful with complete vessel patency	60 (86.96)
Successful with incomplete patency	3 (4.35)
Non successful with major amputation	6 (8.69)

Figure 1



(a) Lower limb before intervention. (b) Twelve-month post-intervention lower limb. (c) The lower limb CT angiography before intervention. (d) Twelve-month follow-up CT angiography. CT, computed tomography.

Figure 2



(a) Upper limb before intervention. (b) 48-h post-intervention upper limb. (c) Upper limb pre-intervention angiography. (d) 48-h follow-up angiography showing complete clot lysis.

On follow-up, five patients showed signs of limb ischemia 9–12 months after intervention; angioplasty and stenting were performed to retain vessel patency with successful revascularization. Three patients died within 7, 14, and 18 months after the procedure (not related to procedure). Kaplan–Meier overall survival among the studied group is shown in Table 4.

Discussion

ALI of the upper and lower extremities remains challenging for clinicians with significant limb loss and mortality. Thrombolysis as a treatment for ALI has become a first-line therapy based on studies published over the last three decades [10].

Prospective randomized trials have shown that the catheter-directed thrombolysis (CDT)-first strategy allows for rates of limb salvage and survival that rival open surgical revascularization. Furthermore, advances in endovascular techniques have made the percutaneous treatment of underlying 'culprit' lesions, thus allowing the treatment of ALI with just an arterial puncture. The results of our study reaffirm the belief that thrombolysis remains a safe and effective alternative to surgery for treating ALI in patients with vasculitis [11].

CDT requires more time than surgical treatment. Therefore, CDT should be considered when there is time, such as in severity classifications 1 and 2 a. In contrast, reperfusion after CDT is slower than with surgical thromboembolectomy and can reduce the risk of ischemia-reperfusion injury. Our study focuses on upper and lower acute ischemia in pure auto-immune non-atherosclerotic patients [12].

Another new technique is ultrasound-accelerated thrombolysis (USAT), which uses sound waves to accelerate thrombolysis. Low-frequency sounds mechanically fragment clots and augment enzymatic fibrinolysis. A recent multicenter, randomized trial

Table 3 Relation between outcome and patient characteristics

Patient characteristics	Good outcome (*N*=49)	Poor outcome (*N*=20)	Test of significance	*P* value
Age (years)				
≤50	26 (53.1)	3 (15.0)	χ^2=8.45	0.004*
>50	23 (46.9)	17 (85.0)		
Sex				
Male	17 (34.7)	10 (50.0)	χ^2=1.39	0.237
Female	32 (65.3)	10 (50.0)		
Etiology				
SLE	23 (46.9)	4 (20.0)		
TAO	9 (18.4)	12 (60.0)	χ^2=15.64	0.001*
Rheumatoid	14 (28.6)	1 (5.0)		
PAN	3 (6.1)	3 (15.0)		
Limb				
Upper	15 (30.6)	4 (20.0)	χ^2=0.802	0.371
Lower	34 (69.4)	16 (80.0)		

χ^2 , χ^2 test; PAN, polyarteritis nodosa; SLE, systemic lupus erythematosus; TAO, thromboangiitis obliterans.*Significant *P* value less than or equal to 0.05.

Table 4 Kaplan–Meier overall survival (month) among the studied group

	Median survival time	SE	95% CI	Log-Rank test	*P* value
Sex					
Male	56.111	1.854	52.47–59.74	0.028	0.867
Female	54.024	1.363	51.35–56.69		
Etiology					
SLE	53.458	1.509	50.50–60.21		
TAO	55.571	2.370	50.92–58.50	0.199	0.905
Rheumatoid	53.200	2.705	47.89–56.41		
Limb					
Upper	55.778	2.160	51.54–60.01	0.035	0.853
Lower	54.180	1.265	51.70–56.65		
Overall survival (month)	55.97	1.145	53.73–58.22	–	–

Log-Rank (Mantel–Cox) was used.CI, confidence interval; SLE, systemic lupus erythematosus; TAO, thromboangiitis obliterans.

compared standard CDT with USAT (EKOS Corporation, Bothell, Washington, USA) in ALI treatment. The results showed that patients treated with USAT achieved revascularization 12 h faster than CDT, with no increase in major adverse effects. Moreover, USAT required significantly fewer units of the thrombolytic agent [13].

Three randomized controlled studies compared surgery with local lysis (STILE, TOPAS, Rochester) in patients with ALI concerning acute treatment success, long-term vessel patency, and amputation-free survival. In all three studies, no significant differences in 30-day limb salvage rates were found. In the TOPAS trial, 1-year amputation-free survival was 65% for local lysis and 69.9% for surgery. The STILE trial reported a significantly higher recurrence of critical limb ischemia following local lysis (64%) compared with surgery (35%), and the amputation rate in the lysis cohort was 10%. These results cope with our study regarding limb salvage and amputation rate, but regarding recurrence of ischemia, our midterm results showed a lower rate of recurrence.

Based on the results of the comparative trials on surgery and local lysis in ALI, the ACC/AHA guidelines have included the following recommendations:

(1) Catheter-based thrombolysis (CDT) is an effective and beneficial therapy. It is indicated for patients with ALI (Rutherford categories 1 and 2a of ALI) of less than 14 days of duration (class 1, level of evidence A).
(2) Mechanical thrombectomy devices can be used as adjunctive therapy for ALI due to peripheral arterial occlusion (class 2a, level of evidence B).
(3) Catheter-based thrombolysis or thrombectomy may be considered for patients with ALI (Rutherford category 2b) of more than 14 days (class 2b, level of evidence B) [13].

Conclusion

CDT in patients with vasculitis with ALI is a safe and effective approach as it gives promising results with a lower risk of major amputation than surgical thrombectomy.

Limitations

The number of patients included in the study was limited as we included only ischemia in patients known to be vasculitis. We need more centers to participate in the study with much more patients and long-term follow-ups to get more accurate results.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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