# Catheter-directed thrombolysis in thrombotic acute lower limb ischemia: challenges and management

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**Background**
The aim of this study to assess the result of catheter directed thrombolysis (CDT) in acute thrombotic lower limb ischemia with special emphasis on the technique and challenges.
**Methods**
It is a prospective study that was held in vascular surgery department, Cairo University from March 2016 to March 2018. Twenty four patients with ALI were recruited with infra-inguinal acute native arterial occlusions less than 14 days. Inclusions criteria were age is less than 75 years, ALI categories I, IIa Rutherford classification. Exclusion criteria were; acute embolic ischemia, ALI category IIb or III Rutherford classification, occluded bypass graft, contraindication of thrombolytic therapy and Patients older than 75 years.
**Result**
Twenty four consecutive patients (19 males and 5 females) were included in the study with mean Age 63.5 years. Out of 24 CDTs performed, 20 patients (83.3%) required additional procedures, 15 percutaneous intervention (12 balloon dilatations and 6 stentings for superficial femoral artery (SFA), and 3 cases of aspiration thrombectomy) and 3 open procedures (3 cases of popliteal thromboemolectomy) and 2 hybrid cases of CFA thromboendarterectomy and angioplasty for femeropoliteal segment). Five bleeding complications were reported in the study group with 4 clinically non- major bleeding complications, all were managed conservatively. Major bleeding from groin required surgical intervention in only one case. A total of 4 (16.6%) major amputations were done during the follow-up period, the amputation-free survival was 87.5%, 83.3%, and 83.3 at one, three, and six months post-procedurally. No mortalities in the study patients during 6 months of follow up.
**Conclusion**
Thrombolytic therapy remains an effective and valuable option for treatment of ALI. About 25% of patients still required an open procedure post thrombolytic therapy. So; proper patients selection is needed to detect patient who will benefit from primary surgery rather than thrombolysis.

**Keywords:**
thrombolysis, thrombotic occlusion, acute limb ischemia

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## Introduction

Acute limb ischemia (ALI) is considered one of the most demanding acute vascular emergencies that requires urgent intervention as it is associated with significant morbidity and mortality. Commonly these patients are critically ill, and open surgery is usually associated with many significant morbidities. Recently, endovascular treatment has been established in the treatment of ALI with reduced morbidity and mortality with good initial results [1]. Currently, thrombolytic therapy as an initial treatment for ALI is generally reserved for patients with Rutherford categories I and IIa ALI less than 14 days duration who do not have significant motor and/or sensory affection [2].

## Patients and methods

This is a prospective study that was held in vascular surgery department, Kasr Al Aini Hospital, Cairo University, over the period of 2 years from March 2016 to March 2018. Of all our cases that presented with acute ischemia of lower extremity in that period, 24 patients were recruited for the study with infrainguinal acute native arterial occlusions.

Inclusion criteria were patients' age less than 75 years old, having ALI categories I and IIa Rutherford classification with symptoms of less than 14 days. All cases that have infrainguinal acute native arterial occlusions were included in the study.

Exclusion criteria were acute embolic ischemia evident clinically and by imaging either arterial duplex ultrasound or computed tomography angiography (CTA), ALI category IIb or III Rutherford classification, occluded bypass graft (vein or graft) and contraindication of thrombolytic therapy, patients older than 75 years old, history of allergy to contrast medium, refusal of consent, or having bacterial endocarditis.

All cases are informed about the intervention and consented before being recruited in the study. Recruited patients satisfying our inclusion criteria are subjected to a thorough history taking and detailed clinical examination.

Preoperative laboratory investigation was done, which included complete blood count, clotting profile, renal function tests, liver function tests, HbA1C, fasting blood sugar, lipid profile, and thrombophilia screen (antithrombin III deficiency test, anticardiolipin antibodies, homocysteine levels, protein C, and protein S), which was done later on to determine the duration of anticoagulation. Detailed cardiac assessment with ECG and echocardiography was adopted to detect any occult myocardial infarction or arrhythmias.

All recruited cases are imaged before intervention using B-mode colored Duplex ultrasound by a skilled sonographer. Its advantages include rapid, radiation-free, noninvasive, and a cost-effective tool. Ankle brachial index (ABI) was recorded primarily. To reduce the unneeded exposure to contrast media, we advocate multi-detector computed tomography (MDCT) angiography and magnetic resonance angiogram (MRA) for selected cases, that is, thrombosed popliteal aneurysm, as they can determine the thrombosed aneurysmal lumen accurately as well as the runoff status. However, digital subtraction arteriography can delineate many essential information, including the site, morphological characteristics of the offending event, runoff status, and inflow and outflow suitability. We preferred to reserve it for our cases when deemed eligible for catheter directed thrombolysis (CDT).

Before the procedure, patients with impaired renal functions should follow renal protection protocol, that is, adequate hydration and administration of N-acetyl cysteine 600 mg Q8 h. All cases before the procedure received a therapeutic dose of unfractionated heparin, which limits the thrombus propagation, protects the collaterals' status, as well as improves the mortality and morbidity rates of the targeted group.

#### Technique

After local anesthesia is given and under ultrasound guidance aided with micropuncture set, 4F (Cook Inc., Bloomington, Indiana), the anterior wall of common femoral artery is punctured anterior to the head of femur in an ipsilateral antegrade approach or in a contralateral retrograde approach. The use of ultrasound-guided puncture with a micropuncture set helps to reduce the possibility of groin and subsequent retroperitoneal hematoma.

Choice of the approach depends on the morphological data for the occlusion offered by duplex ultrasound, the presence of hostile groin, and patients with obesity with pendulous pannus. With either approach, a 6F sheath is placed at the puncture site, and in cases in which a contralateral approach is needed, a cross-over sheath, Balkin (Cook Inc.) is used, where its tip is aimed at common femoral artery of the targeted limb. A 5000 IU heparin dose is administered via sheath accordingly.

Initial angiogram of the targeted limb is carried out with the least possible contrast injections and using digital subtraction arteriography with delaying imaging to assess tibial runoff status. Tibial run off status and whether it is continuous with the foot vascular arch or not is assessed and recorded for each patient before catheter-directed thrombolysis. We believe in that this angiographical note may affect the outcome of CDT in such cases.

Guide wire traversal test is carried out after delineation of the morphological status of the occlusion using a soft J tip wire, that is, Rosen wire (Cook Inc.). A soft J tip is needed to avoid inevitable dissection in a blind occluded infrainguinal segment. Easy passage of the wire through the clot predicts a good response to CDT. The results of guide wire traversal test are recorded initially for each patient. For cases with difficult passage of guide wire, we consider least number of trials to avoid devastating complications and will only try to place our catheter for thrombolysis in the proximal end of the targeted occlusion hoping for some lysis after initiation of the therapy some hours later that can give a chance to the guide wire to easily

pass through the occlusion during a follow-up angiogram; otherwise, the intervention will be abandoned for these cases.

Then a multi-side-hole infusion catheter, namely, Fountain (Merit Medical Systems Inc., South Jordan, Utah, USA) or Unifuse (Angiodynamics) with different infusion segment lengths according to the length of the targeted occlusion is advanced through the occlusion and secured in position under fluoroscopy.

Patients are sent back to ICU for continuous tight monitoring of the vital signs, complete blood count, and serum fibrinogen. We adopted the use of intrathrombus high-dose bolusing or lacing followed by low-dose continuous infusion of Alteplase [recombinant tissue plasminogen activator (rtPA)] in all cases as follows: bolus dose at 5–10 mg, and then continuous infusion at 0.5–1.0 mg/h (40 mg maximum). An infusion dose of 500 IU/h unfractionated heparin through the sheath is initiated to avoid subsequent sheath thrombosis. After 24-h duration of initiation of the lytic therapy, patients are returned to the angio-suite, and a follow-up angiogram is obtained.

#### Definitions and end points

Technical success is complete lysis of the thrombus more than 95% or near complete lysis more than 70% by angiographic measurements in the native infrainguinal artery without uninterrupted flow in at least 1 crural vessel without distal thromboembolic complication

Clinical success is the relief of acute ischemic symptoms.

The procedural end points include technical success, clinical success, presence of residual thrombus or plaque, occurrence of a major complication, that is, severe bleeding with abortion of the procedure, failure of CDT progression despite full dose of lytic therapy has been reached, progression to Rutherford category III with signs of muscle rigor, and failure of guide wire traversal test.

After thrombolysis, offending lesions in the native arterial tree should be dealt with accordingly with percutaneous transluminal angioplasty (PTA) with or without stenting. In case, there is a residual thrombus or plaque, and this can be removed either surgically with balloon thromboembolectomy or with adjuvant percutaneous aspiration.

**Table 1 Demographic, associated comorbidities, clinical characteristics and CDT variables**

| Variables of CDT | *n* (%) (*N*=24) |
|---|---|
| Smoking | 16 (66.6) |
| Hypertension | 15 (62.5) |
| Diabetes mellitus | 12 (50) |
| Ischemic heart disease | 11 (45.8) |
| Respiratory disease | 3 (12.5) |
| Cerebrovascular disease | 3 (12.5) |
| Renal insufficiency | 2 (8.3) |
| Occluded segments | |
| Femoral | 4 (16.6) |
| Femoropopliteal | 15 (62.5) |
| Tibial | 5 (20.8) |
| Lytic therapy alone | 4 (16.6) |
| Lytic therapy+open procedures | 3 (20.8) |
| Lytic therapy+endovascular procedures | 15 (62.5) |
| Lytic therapy+hybrid procedures | 2 (8.3) |
| Bleeding complications | 5 (20.8) |
| Minor bleeding | 4 (16.6) |
| Major bleeding | 1 (4.2) |
| Primary patency after 6 months | 20 (83.3) |

CDA, catheter directed thrombolysis.

Postoperatively patients are maintained on dual antiplatelet therapy for 4 weeks, that is, aspirin (81 mg daily), and clopidogrel (75 mg daily), and then on one antiplatelet therapy, that is, aspirin (81 mg daily) for life.

For cases that proved to be embolic and/or thrombophilic, they are given therapeutic heparin doses and then maintained on oral warfarin for life.

Patients are followed in the outpatient clinic at 1, 3, and 6 months clinically, and ABIs, arterial duplex ultrasound, and CTA were done when needed.

#### Ethical committee

This study has been approved by our institutional research ethics committee. Funding was obtained from Cairo University Hospitals, though it had no role in study design, collection of data, and its analysis.

## Results

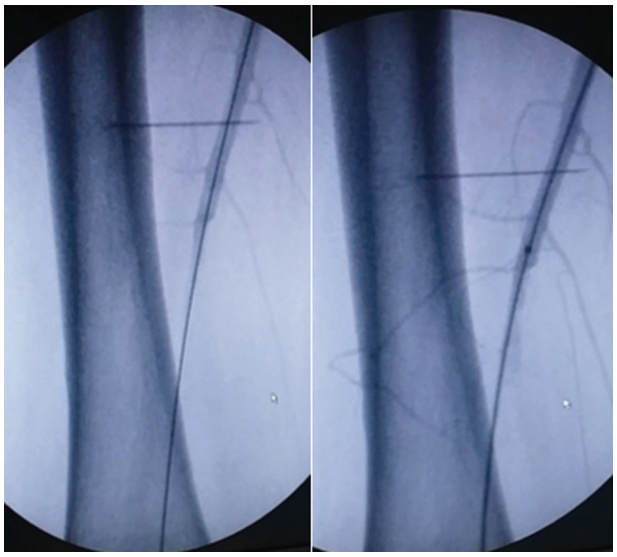
Demographic, associated comorbidities, clinical characteristics, and CDT variables are shown in Table 1.

Twenty-four consecutive patients (19 (79%) males and five (21%) females) were included in the study with mean age of 63.5 years. Of 24 CDTs performed, 20 (83.3%) patients required additional procedures to obtain adequate distal perfusion to the foot upon completion of the procedure. These modalities included 15 percutaneous intervention (12 balloon dilatations and six stentings for superficial femoral artery (SFA) lesions

**Figure 1**

Left SFA occlusion.

**Figure 2**



Intraoperative angiography.

after unsatisfactory results with balloon dilatation alone and three cases of aspiration thrombectomy), three open procedures (three cases of popliteal thromboembolectomy after failed aspiration thrombectomy), and two hybrid cases of CFA thromboendarterectomy and patch closure with angioplasty for femoropopliteal segment.

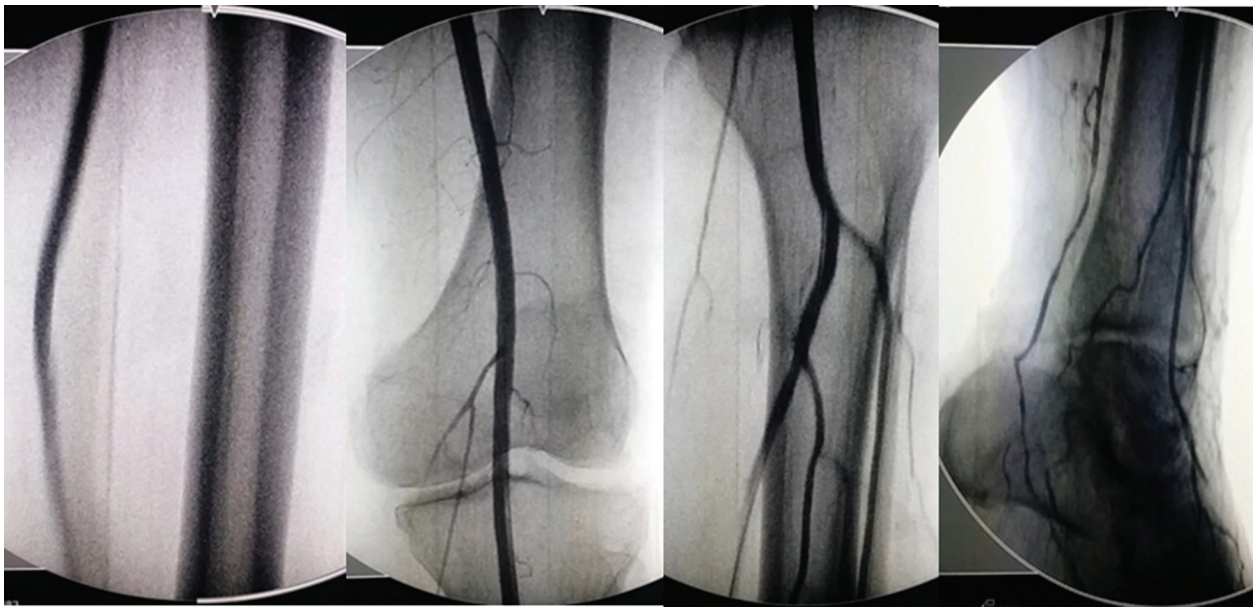
**Figure 3**

Intraoperative angiography with infusion catheter in the thrombotic occlusion.

All patients included in the study presented within 14 days from ALI onset with mean duration of 6.2 days, with 16 (66.6%) patients of class I and eight (33.3%) patients of class IIa Rutherford grade for ALI. The mean duration of thrombolytic therapy was 1.5 days.

Five bleeding complications were reported in the study group, with four clinically relevant nonmajor bleeding complications (20.8). There were two cases of groin hematoma (one ipsilateral and one contralateral; related to the access used) and a single case of gingival bleeding; all were managed conservatively and none had received blood transfusion. The remaining female patient developed vaginal bleeding with hemoglobin drop of 1 g/dl in 3 days, related to anticoagulant therapy, and this was managed conservatively. Major bleeding from groin, requiring an early stop of the CDT, a blood transfusion, and surgical intervention, required control of bleeding combined with thigh fasciotomy in only one of the cases. Additionally, no patients developed an intracranial hemorrhage. None of the patients experienced allergic reactions or contrast-induced nephropathy.

**Figure 4**



Completion angiogram after CDT from SFA, popliteal to pedal vessels.

A total of four (16.6%) major amputations were performed during the follow-up period, and three (12.5%) of these were performed within the first month from the procedure, when sufficient distal perfusion could not be achieved even after femorodistal bypass after failure of thrombolytic therapy. The amputation-free survival was 87.5, 83.3, and 83.3% at 1, 3, and 6 months postprocedurally. There were no mortalities in the study patients during the 6-month follow-up (Figs 1–4).

## Discussion

Open surgical thromboembolectomy with or without bypass procedures was the standard of care for ALI; whilst with the recent advances of endovascular therapy, catheter-directed thrombolysis has been increasingly used as a first option. This may be owing to more advancement with endovascular techniques with less morbidity, mortality, avoidance of general anesthesia, and early recovery with these minimally invasive interventions in very high-risk fragile patients [3].

Currently, CDT as an initial intervention for ALI is generally indicated for patients with Rutherford classes I and IIa, where there is no significant motor and/or sensory affection, with symptoms less than 14 days [4].

The mortality, complication rates and hemorrhagic stroke risk in this study were nearly comparable to previous randomized trials. The Rochester, STILE and TOPAS 2 trials have showed a mortality rate of 4% to 20%, compared to 4.9% in our study. We do not have any major intracranial bleeding and it could be attributed to that we exclude all patients above 75 years old with high rate of intracranial bleeding. However, major intracranial bleeding was reported by some studies to range between 1.2% to 2.3% [6–8].

The risk of bleeding associated with intra-arterial thrombolysis is quite concerning especially local bleeding from the puncture site, however, local bleeding complications in our study were mild and managed conservatively without surgical intervention. Few bleeding episodes required blood transfusion (one patient, 4.2 %) or thrombolysis to be discontinued (2 patients, 8.3%) [13]. Aggressive thrombolysis is associated with high bleeding complications, but lower amputation rate. So, to achieve optimal limb salvage, you have to accept minor bleeding complications [13].

A higher rtPA dose can achieve successful thrombolysis, an advantage in acute severely ischemic patients. But, this is counterweighted by increased bleeding complications. *The Study of The Thrombolysis or Peripheral Arterial Surgery (TOPAS) trial* has documented major bleeding complication rate at 12.5%, intracranial bleeding 1.4 %. The only predictor for hemorrhagic strokes complication in most of studies was older age, with all hemorrhagic stroke patients aged more than 70 years [11].

In the current study, heparin was used in a small dose (400 IU/h) to avoid thrombosis around the sheath. However, heparin usage was associated in some studies with increased bleeding risk as in the Thrombolysis or Peripheral Arterial Surgery (TOPAS) trial. On comparing thrombolysis with surgery for acute lower limb ischemia, heparin was found to be an independent risk factor for major hemorrhage. Owing to the high rate of intracranial hemorrhage, heparin use was stopped prematurely in the trial. Stroke occurred in 1–2% of the procedures [11].

The rate of amputation and fasciotomy was higher in the group that underwent open surgery after failed thrombolysis than the group that had direct surgery from the beginning; this could be explained by thrombolysis trashing to the outflow arteries and bleeding complication intraoperatively and after surgery from lytic effect on fibrinogen and other hemostatic pathways. Other risk factors that were associated with poor outcome were old age and atrial fibrillation, which were associated with death within 5 years from thrombolysis for ALI [9].

We excluded the occluded bypass from analysis, as there is worse outcome with occluded bypass, presumably owing to endothelial alteration in vein bypass and added proximal neointimal hyperplasia in both vein and synthetic graft bypasses to avoid confounder and to know the actual effect of thrombolysis in ALI.

The reported amputation-free survival rate of 83.6% in this study is similar to that in previous reports [12].

## Conclusion

Thrombolytic therapy remains an effective and valuable option for treatment of ALI, it is associated with improved outcomes with low incidence of major bleeding complications. However, open surgery after failed thrombolysis has higher amputation rates, 25% of patients still required an open procedure post thrombolytic therapy. So; proper patients selection is needed to detect patient who will benefit from primary surgery rather than thrombolysis.

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Nil.

### Conflicts of interest

There are no conflicts of interest.

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