

Catheter-directed intra-arterial thrombolysis for lower extremity arterial occlusions

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ABSTRACT

Catheter-directed intra-arterial thrombolysis (CDT) is a rational treatment method in patients with acute/subacute and even some chronic occlusions of lower extremity arteries and bypass grafts having salvageable limb ischemia. Immediate vessel patency can be achieved with an acceptable complication rate in many patients, especially those with fresh thrombus or emboli. It can be also an adjuvant treatment modality for endovascular interventions for chronic occlusions. There is no standard method of CDT including thrombolytic agent dose and technique. Selection of treatment strategy should be based on individual judgment based on viability of limb, lesion characteristics, and risks of hemorrhage. (*Anatol J Cardiol* 2019; 22: 54-9)

Keywords: acute limb ischemia, catheter-directed thrombolysis, peripheral artery disease

Introduction

Peripheral artery disease (PAD) may be asymptomatic, may limit exercise capacity due to claudication, or may even lead to limb amputation. Although general underlying mechanism is atherosclerosis, thrombosis is also a common finding in case of recent onset of symptoms, especially in patients with acute limb ischemia (ALI) (1). ALI may also be caused by cardiac emboli, embolization from aneurysmal thrombus, and peripheral bypass graft thrombosis. During arterial catheterization, iatrogenic causes may also lead to fresh thrombus formation. Since there's not enough time for distal collateral development, acute emboli usually present with abrupt onset of serious symptoms.

Surgery, percutaneous intervention, and catheter-directed thrombolysis (CDT) are the potential strategies for the restoration of distal perfusion of lower extremities in such cases. Surgical revascularization may be associated with increased mortality as high as 25% (2). CDT through a catheter directly into the thrombosed portion of the vessel is more effective and safer than systemic thrombolysis. Bleeding complications are fewer and minor due to lower doses. Therefore, CDT represents a potential alternative to surgery. General anesthesia and its risks are avoided in patients with PAD, a group of patients who have comorbidities for increased mortality with surgery (3, 4). Among

other potential advantages of CDT are avoidance of endothelial injury owing to lack of mechanical trauma, dissolution of thrombus even in the distal territory of the occlusion, and reduced risk of rethrombosis. CDT may be achieved with just thrombolytic agents or in combination with pharmacomechanical interventions. With resolution of thrombus, CDT may uncover the underlying atherosclerotic stenosis, and therefore, may aid in selection for subsequent appropriate interventional treatment modalities (5, 6). The CDT has become widely-used in 90s following publication of the Rochester (7), STILE (8), and TOPAS trials (9). After documentation of compatible results of CDT with operation in such randomized trials, it was considered as a first-step treatment option for ALI patients with ischemia symptoms of <14 days duration. A consensus published in 2003 concluded that CDT can be used for resolution of acute thrombus or emboli material and restoration of perfusion. Since then, however, current thrombolytic agents and techniques of administration have changed significantly (10).

Recombinant tissue plasminogen activator

Thrombolysis is the therapy of choice in the case of occlusions of distal stream bed or branches of main vessel by lysis and fragmentation of thrombus. Thrombolysis may be able to achieve recanalization of even distal small runoff vessels (11).

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Among thrombolytic agents, streptokinase fell into disuse due to high frequency of allergic reactions and relatively higher bleeding rates. Urokinase is no longer available in the market. Today, the easily available plasminogen activator agents include alteplase [recombinant tissue plasminogen activator (rtPA)] or its mutant derivatives. Tissue plasminogen activator converts plasminogen to plasmin. Plasmin then degrades fibrin polymers and lyses thrombus. Half-life of tPA is 4–7 min in circulation. When it is bound to fibrin, its efficacy increases $\times 400$ times compared with freely circulating tPA (12, 13). Therefore, benefit of the agent seems greater when it is delivered into the thrombus. Thus, infusion of tPA directly to thrombus will reduce the dose and avoid the systemic complications (14).

Catheter-directed thrombolysis technique and thrombolytic agent dose

Usually, the infusion catheter is advanced to the level of the thrombosis through a crossover catheterization from a contralateral common femoral artery puncture. Sometimes, left brachial artery, the ipsilateral common femoral artery, or popliteal artery is used for sheath insertion. To accommodate the 5 Fr lysis catheters and to allow aspiration, angioplasty and stent placement at least a 6 Fr sheath is recommended. In order to provide maximum exposure of thrombolytic agent to the thrombotic burden in the artery with the least applicable dose, the highly concentrated agent is usually delivered by a special catheter lodged within the thrombotic lesion. This also provides delivery of the agent directly to the vicinity of thrombus bound plasminogen. An easy traverse of the occlusion by guidewire is a marker of soft thrombotic lesion. In this case, thrombolysis is more likely to dissolve clots (13, 15). A multi-side holed end-hole occluded infusion catheter (i.e., Cragg–McNamara, Unifuse) should be placed along the length of the occlusion when a guide wire is advanced from the occlusion toward distal runoff vessel. If the occlusion cannot be crossed with wires, then an end-hole catheter can be located proximally to the occlusion and thrombolysis initiated. For direct exposure of agent to the thrombotic cap, side branches between the tip of the catheter and the occlusion should be avoided. In some cases, occlusion can be crossed with a guide wire after softening of proximal thrombotic cap following several hours of thrombolysis.

There is no standard method of CDT including thrombolytic agent dose and technique. There are several notable thrombolytic delivery methods: continuous infusion, bolusing, pulse spray, graded infusion, and stepwise infusion (11). Currently, the simplest and most commonly performed method is continuous infusion. Thrombolytic agent may be infused slowly through a multi-side hole catheter (i.e. Crag–McNamara infusion catheter). In the bolus method, a single highly concentrated dose of thrombolytic agent is delivered throughout the occlusion and then continuous infusion is initiated. In the pulse spray method, small amounts of thrombolytic agent are injected repeatedly with forceful injections. Pulse spray is performed in the cath lab till antegrade flow

is restored. Compared to slow continuous infusion, pulse spray thrombolysis can achieve distal flow more rapidly. However, cath lab is occupied and distal embolization rate is higher. In graded infusion, drug infusion rate is reduced gradually. In stepwise infusion, the effect of thrombolytic is controlled with contrast injection after a short infusion through an end-hole catheter adjusted close to the thrombus. If proximal portion of thrombotic lesion is lysed, the catheter is repositioned forward repeatedly until recanalization. Since continuous infusion requires the least procedure time, it is an appropriate choice if there's no immediate revascularization indication. After a low dose and slow 12–24 hours infusion a control angiography can be performed next day. The bolus or pulse spray methods may be preferred when time is limited to achieve antegrade flow (16-18). Multi-side hole catheters are simple to use, and compared to end-hole catheters, they tend to be more stable and provide throughout exposure of thrombus to the evenly dispersed thrombolytic agent. Half-life of tPA in circulation is very short and it dramatically increases when it is jailed in thrombus (19). The space for thrombolytic agent in the thrombus is too limited. A higher diluted amount than the thrombus can accommodate will result in more drainage into systemic circulation. Therefore, thrombolytic agent should be given in the highest possible concentration to be in face with thrombus exclusively. The higher the volume infused (the more the tPA is diluted), the more fluid (and therefore tPA) will drain out with a higher risk of systemic bleeding. The volume of a 10 cm length thrombus in the superficial femoral artery is about 3 mL. If more than 1 mL is injected abruptly, it is highly probable that a significant portion would drain into the general circulation. Yet, some practitioners have been recommending performance of first bolusing dose of thrombolytic agent to be dissolved in 50 to 80 mL of fluid (13). Different dosage schemes of rtPA have been applied varying from 0.05 to 0.1 mg/kg/hour and from 0.25 to 10 mg/hour. Generally, higher doses of rtPA have not found to be more beneficial. Commonly used alteplase dose today is: continuous, 0.5 to 1.0 mg/kg/h (40 mg maximum); bolus, 2 to 5 mg bolus, then continuous infusion; pulse spray, 0.5 mg/mL at 0.2 mL every 30 to 60 seconds (11, 20). In our daily practice, we generally apply continuous infusion method after 3–5 mg bolus injection, and have gradually decreased infusion dosage from 2 mg/h to 0.5 mg/h by the time. With reduced dose infusion, we have observed same efficacy with lower bleeding rates.

Heparin infusion during thrombolysis

The potential benefits or harms of simultaneous heparin infusion during CDT have not been well-established. It has been suggested that concomitant heparin administration may prevent pericatheter thrombosis. Alteplase and heparin should be infused separately since they will precipitate when mixed together (21). Heparin can be administered either intravenously or through a proximal sheath around the catheter (11, 12). However, it has been suggested that use of therapeutic heparin doses in conjunction with tPA-derived lytic agents has increased bleed-

ing complications without improved efficacy. Usually, a sub-therapeutic dose between 200 and 500 U/hour producing a mild prolongation of aPTT, is commonly used. Although some practitioners do not advice to monitor aPTT values, others do due to uncertainty of heparin dose response. Recently, it has been reported that, concomitant continuous heparin infusion during thrombolysis was associated with more bleeding complications and offered no short- or long-term benefit (22).

The results of catheter-directed thrombolysis

Catheter-directed thrombolysis is a rational treatment method in patients with acute/subacute and even some chronic occlusions of lower extremity arteries and bypass grafts having salvagable limb ischemia (Fig. 1). Selection of potential responders for CDT and avoidance of bleeding complications, especially hemorrhagic stroke, is crucial. Compared with surgical intervention, CDT has been reported to have similar limb salvage rates and lower mortality rates at 12 months (23) Reported success rates with CDT are inconsistent with a wide range (38%–91% for occlusions of <3-month duration) which may be due to differences in individual and lesion characteristics (15). Compared to bypass grafts, higher technical success was reported for native arteries in some studies (24, 25), whereas better results were reported for bypass grafts in others (26). And some authors have found no difference between native arteries and bypass grafts (19). As well as immediate success rate (86.7%) long-term primary patency is also higher in embolic occlusions (27). In the Rochester trial, 114 patients with limb-threatening ischemia of <7 days' duration were randomized to thrombolytic therapy or surgical therapy. Thrombolytic therapy was able to dissolve thrombus completely in 70% of the cases. Although limb salvage rate was not different between the groups, mortality rate was significantly lower in the thrombolysis group at 12 months (19).

In STILE trial patients with symptoms for <14 days, limb salvage was significantly higher with percutaneous thrombolysis (89% vs. 70%) with a trend toward lower all-cause mortality during 6-month follow-up. Nevertheless, hemorrhagic complica-

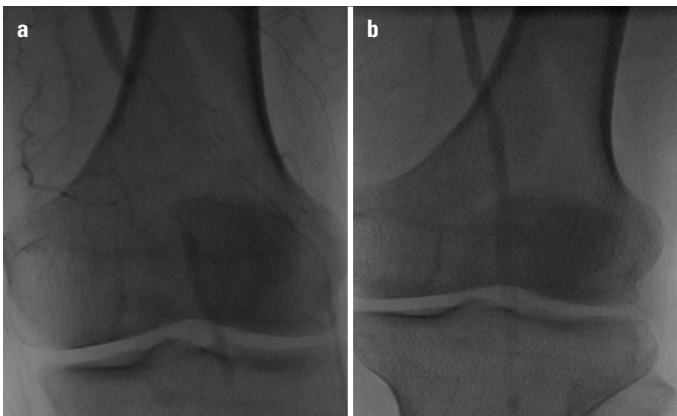


Figure 1. Total occlusion of distal superficial femoral artery (a). Complete resolution of thrombus and restoration of distal flow after catheter-directed thrombolysis with 1 mg/h t-PA infusion for 20 hours (b)

tions were unacceptably higher with thrombolysis and ongoing ischemia frequency was less with surgery (8). TOPAS trial randomized patients having ALI with symptoms for <14 days (native arterial or bypass graft occlusion) to CDT (urokinase) or surgery. Although limb salvage rate at 12 months were similar (65% vs. 69.9%), major bleeding was significantly more frequent in the CDT group (12.5% vs. 5.5%; $p=0.005$). In the post-hoc analysis, limb salvage rates were found to be higher with thrombolysis, whereas surgery was superior in shorter occlusions (9). Grip et al. (27) reported long-term results of 689 procedures. During a mean follow-up of 59.4 months, 50.7% of the patients had no reintervention, 16.4% underwent amputation without reintervention, and reintervention was required in 32.9% of the patients. The rate of reintervention was 16.3% in the embolus group, 25.4% in the thrombosis group, 34.0% in the popliteal aneurysm group, and 48.0% in the graft or stent occlusion group. Overall primary patency rate was 69.1% at one year and 55.9% at 5 years. Five year primary patency was 83.3% for the embolus group and 43.3% for the occluded graft/stent group (27).

In addition to in acute occlusions with thromboembolism in native vessels, CDT is also useful for some chronic occlusions and native bypass graft occlusions. History of long duration of symptoms suggesting chronicity is not a contraindication for thrombolysis. In some chronic cases, a trial of CDT may be reasonable regardless of the symptom duration or the time of diagnosis of the occlusion. There are cases in which CDT was intended for bypass graft occlusion, but native arterial occlusion was lysed instead. Thrombolytic therapy may enhance the ability to perform angioplasty of lesions which are considered difficult. For instance, CDT was able to resolve an osteal blunt stump and aided us to continue intervention antegradely. A trial of thrombolysis by CDT may soften and shorten the occlusion, aiding in crossing the wires and balloons. Furthermore, based on the new appearance of the shortened and clearer underlying lesion, the choice of decision for the treatment approach with percutaneous intervention or surgery would be more accurate. Therefore, technical success and patency would be better in the management of post-thrombolytic smaller lesion (28).

Thrombolysis of chronic occlusions of the tibial arteries is not as successful as in larger arteries. However, such patients are poor candidates for surgery due to absence of a good distal bypass target. Therefore, patients, especially those having acute onset of symptoms with suspected emboli or fresh thrombus in infrapopliteal tree, should be offered CDT. We have also experienced complete or near-complete lysis of thrombin in such below the knee occlusions (Fig. 2).

Thrombolysis is quite successful in large vessels like abdominal aorta and iliac arteries. Besides acute occlusions, chronic occlusions of the common femoral, superficial femoral, and popliteal arteries may be treated with CDT. This better result may be secondary to the presence of softer, less-organized, and partially thrombotic areas in large vessel occlusions. Supporting this finding, in some chronic cases, even a hydrophilic

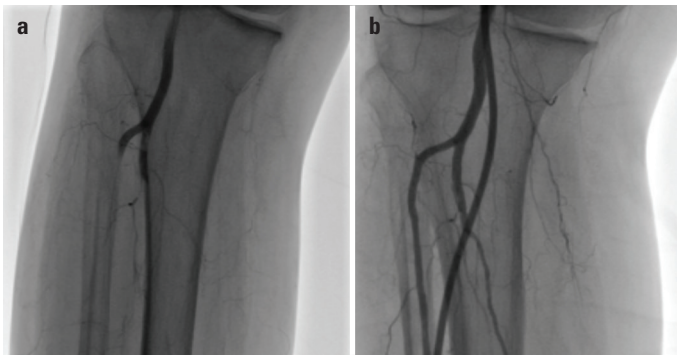


Figure 2. Total occlusion of below the knee (a). Complete resolution of thrombus and restoration of distal flow after catheter-directed thrombolysis with 5 mg bolus injection and 1 mg/h tPA infusion for 24 hours (b)

wire easily passes through chronic occlusions of those large vessels. Thrombolysis may aid consequent percutaneous intervention via softening lesion or eliminating thrombus burden. It may also improve the long-term patency via limiting angioplasty or stenting to a shorter atherosclerotic segment instead of a long-segment (29). Cost-effectiveness and patency rates were reported to be better with CDT in non-embolic occlusions due to correction of the underlying disease after thrombolysis (30). Furthermore, thrombolysis may be useful after fragmentation of atherothrombotic lesion by angioplasty. In addition to the proximal part of underlying atherosclerotic occlusion, thrombus may also be present at the distal part. Therefore, thrombolytic agent may not reach through underlying calcific atherosclerotic lesion toward distal thrombus. Increasing the area of exposure between the clot and the thrombolytic agent may not be essential for a fresh clot, but it is an important consideration in the treatment of chronic occlusions. Thus, thrombolysis after clot fragmentation/maceration with angioplasty is effective and necessary for adequate dissolution of thrombus. We and other practitioners have

observed the resolution of residual thrombus after angioplasty of chronic long occlusions (Fig. 3 and 4) (31).

Complications

The most frequent complication of CDT is bleeding. These bleeding complications are usually minor and can be controlled without interruption of thrombolysis. One of the most feared complications is intracranial hemorrhage, with a frequency of 0.4%–1.2% (6, 27, 32). A meta analysis of 1283 patients in five randomized trials comparing intra-arterial thrombolysis and surgery incidences of major hemorrhage and stroke were 8.8% and 1.2% (32). For bleeding complications of thrombolysis, concomitant heparin therapy is used. Avoiding heparin infusion or preference of subtherapeutic heparin dosage may decrease the frequency of bleeding complications. Furthermore, there's doubt about the short- or long-term advantages of concomitant heparin infusion (22). Minor bleeding usually occurs around arterial puncture sites. Pressure or exchange of the sheath with a wider one is usually effective in the management of pericatheter bleedings. In the case of major bleeding complications, thrombolytic and heparin infusions should be halted. Fresh frozen plasma should be administered to refresh fibrinogen and other clotting factors. Related departments should be consulted emergently (i.e. cardiovascular surgery for arterial repair, general surgery for retroperitoneal hematoma). Additional endovascular balloon dilatations and stentings or minor surgical procedures like endarterectomies, open angioplasties, and/or short-segment jump bypasses may be performed in the case of CDT failure or inadequate result (33).

Reperfusion syndrome may occur in case of prolonged and severe ischemia. Reperfusion syndrome may be limited as a local response (limb swelling which may potentially aggravate tissue injury) or may result in a systemic response leading to multiorgan failure and death. Metabolic abnormalities like acidosis, acute

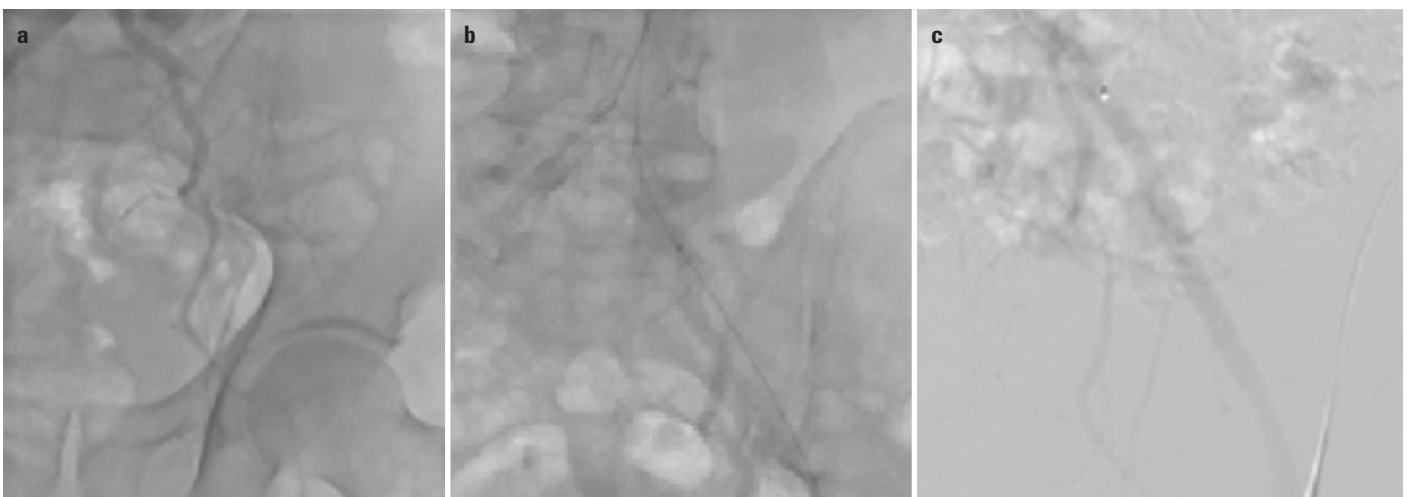


Figure 3. Total occlusion of left external iliac artery (a). After thrombus fragmentation and achievement of distal flow with balloon angioplasty (b) catheter-directed thrombolysis with 1 mg/h tPA infusion for 24 hours was performed after 5 mg bolus injection. Complete resolution of thrombus and restoration of distal flow (c)

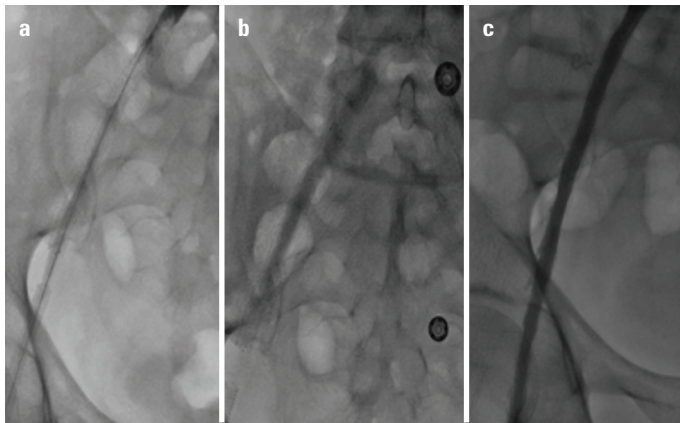


Figure 4. In stent restenosis in common iliac to common femoral artery (a). Inadequate result after balloon angioplasty (b). Successful lysis of thrombi and recanalization after catheter-directed thrombolysis with 1 mg/h t-PA infusion for 20 hours (c)

renal failure, respiratory distress, disseminated intravascular coagulation, and severe hypotension are among common systemic sequelae. In case of systemic response, the mortality rate with reperfusion syndrome is too high. Systemic effects may be more dominant, especially in thrombosis of larger vessels like aorta and main iliac arteries. The slow gradual lysis of thrombus with continuous CDT method allows the toxic metabolites to be mobilized slowly. Therefore, the patient may tolerate the systemic effects more easily compared to immediate achievement of recanalization by surgery or intervention (34). We had an experience of subacute thrombotic occlusion of distal abdominal aorta treated with CDT in which the patient had a sudden onset of respiratory arrest after 8 hours of onset of intra-arterial tPA infusion.

Distal embolization from iliac or femoral arteries can be managed by maintenance of selective thrombolytic infusion with a microcatheter in the occluded distal popliteal or infrapopliteal arteries. In some cases, we had experienced distal embolization of thrombus after angioplasty or tPA bolus and following CDT with continuous infusion was successful in complete or near-complete lysis of distal embolization in those cases (Fig. 5).

Conclusion

In conclusion, instead of surgery, CDT combined with or without endovascular approaches is an effective rational treatment option for many patients with ALI. Immediate vessel patency can be achieved with an acceptable complication rate in many patients, especially those with fresh thrombus or emboli. It can be also an adjuvant treatment modality for endovascular interventions for chronic occlusions. Selection of one treatment strategy over another should be based on individual judgment based on viability of limb, lesion characteristics, risks of hemorrhage, and general anesthesia.

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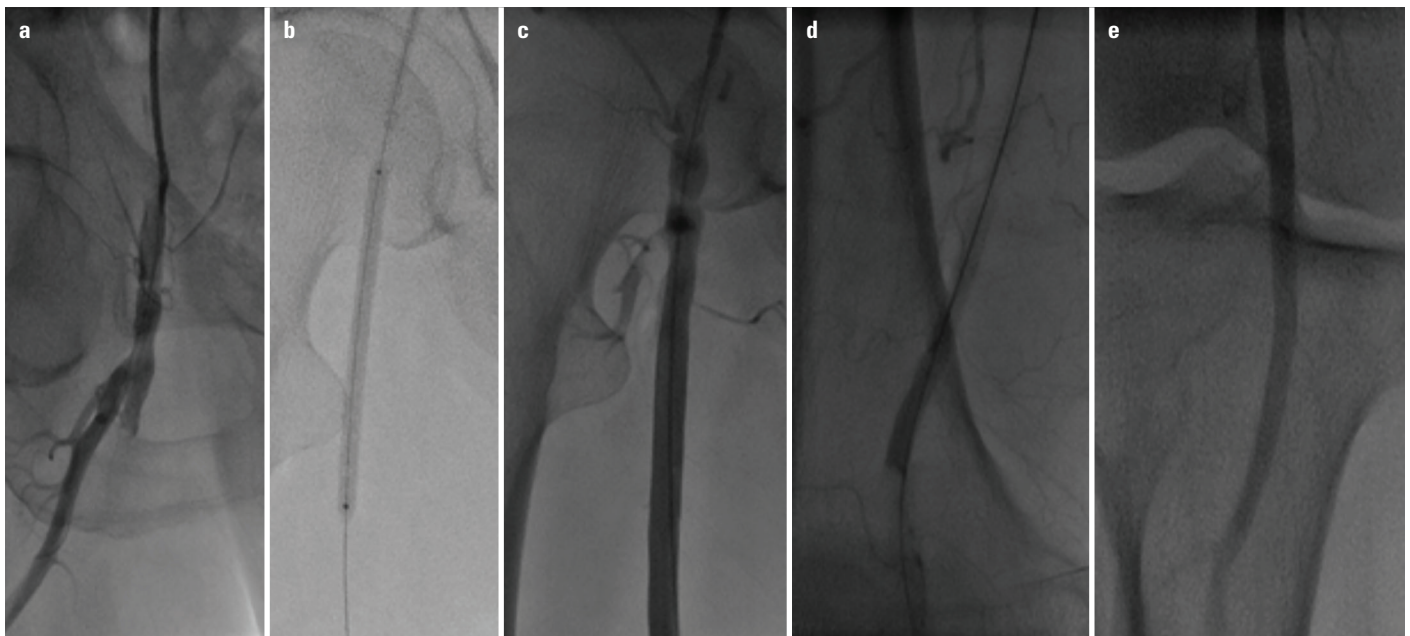


Figure 5. Chronic occlusion in proximal superficial femoral artery (SFA) (a). Balloon angioplasty (PTA) (b). PTA was successful for recanalization of proximal SFA (c). However, distal embolization and occlusion popliteal artery is observed (d). Following catheter-directed thrombolysis with 1 mg/h t-PA infusion for 20 hours distal flow was achieved (e)

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