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Original Research Article

Catheter directed thrombolysis in management of early acute thrombotic ischemia: early experience

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ABSTRACT

Background: To assess the effectiveness of catheter directed thrombolysis in management of early acute thrombotic ischemia.
Methods: A prospective study was carried out on 18 patients (13 males, 5 females) with a mean age of 49 years (ranged from 45 - 69 years) suffered from acute thrombotic lower limb ischemia (Rutherford II- a) and submitted to catheter directed thrombolysis (CDT) using tissue plasminogen activator (TPA) between August 2015 to March 2017. The commonest thrombosed artery was superficial femoral artery (SFA). Major risk factors were diabetes and smoking (66% and 56%) respectively. The infusion method was lacing technique followed by continuous infusion.
Results: Technical success was obtained in 15 patients (83%). Complementary revascularization was performed in 5/15 patients (33.3 %) by balloon angioplasty. Limb salvage rate at 6 months was (77.7%). Failure of thrombolysis occurred in 3 limbs (16.6%); one patient treated by femoro-popliteal bypass while the other two limbs ended by amputation. Regarding complications, bleeding (local groin hematoma or minimal retroperitoneal hematoma) occurred in 3 patients (16.6 %). No major bleeding was recorded. Amputation had performed in 2 cases (11%) while mortality rate within 6 months was 16.6 %.
Conclusions: With proper patient selection, CDT should be considered the first-line treatment for patients with (Rutherford II- a) acute thrombotic limb ischemia.

Keywords: Acute thrombotic ischemia, Catheter directed thrombolysis

INTRODUCTION

Acute limb ischemia (ALI) is a vascular emergency carries high risk of mortality and limb amputation. It is described by sudden loss or marked decrease in limb perfusion that threatens limb viability.[1] The incidence is about 1.5 cases per 10000 persons per year.[2] Thrombotic occlusion is the commonest variety of acute limb ischemia.[3] It occurred in any segment of lower limb but most commonly affect superficial femoral artery (SFA).[4] Disruption of atheroma plaque and platelet aggregation to the exposed surface coupled with stasis of flow will initiate thrombosis. The thrombus usually extends proximally from site of the lesion to the adjacent segment.[3]

Management of acute ischemia depends mainly on the clinical status of the limb and associated patient comorbidity. Outcomes and prognosis largely depend on rapid diagnosis and initiation of proper and effective therapy.[5] Systemic administration of thrombolytic agents to treat ALI carries a significant morbidity and mortality with poor clinical results so it is not recommended while current methods include CDT and pharmacochemical thrombolysis are recommended. Achievement of

successful management requires proper patient selection and wise clinical assessment.[6]

CDT provides thrombolysis of the thrombosed portion and unmask the hidden underlying lesion that can be treated either by endovascular techniques or surgically. In many patients, thrombolysis followed by endovascular interference can decrease the need for surgery.[7] CDT is considered the recommended treatment for selected patients suffering from acute thrombotic ischemia when the thrombolytic therapy is not contraindicated.[8]

METHODS

This prospective study was carried out from August 2015 to March 2017 in Sohag University Hospitals on 18 patients (13 males, 5 females) with a mean age of 49 years (ranged from 45 - 69 years) suffered from acute thrombotic lower limb ischemia (Rutherford II-a). Exclusion criteria were; high risk patients to thrombolytic agents, patients that couldn't tolerate the anticipated time of treatment, the thrombus burden wasn't suitable for thrombolysis in a reasonable short time, patients unfit for interventional radiology e.g. renal insufficiency, contrast hypersensitivity or pregnancy. All patients were admitted and signed an informed consent before treatment. Prior to thrombolysis, full clinical assessment was carried out including detailed history taking and examination including onset of complaint, history of caudication pain, risk factors e.g. diabetes mellitus (DM), smoking, cardiovascular, cerebrovascular diseases, previous vascular medication, endovascular intervention or bypass surgery.

All patients were subjected to thorough physical examination regarding absent pulsation, manifestation of acute ischemia with special concern to muscle weakness, level of paraesthesia, coldness, capillary refilling, ankle pressure measurement, mottled skin and duplex ultrasound imaging. CT angiography was performed to all cases for diagnosis, detection the site of thrombosed vessels and plan of proper access. All patients had undergone full laboratory investigations especially renal functions and coagulation profile.

Figure 1: Totally occluded SFA artery.

Procedure details: The procedure was operated under local anesthesia in all cases. Ipsilateral or contralateral femoral arterial puncture was done and 5000 IU heparin after sheath insertion was injected before staring the procedure. Pre-intervention angiography was performed to assess the location of the thrombus and distal run-off prior to intervention (Figure 1, 2, 3). 0.035 hydrophilic guide wire was traversed and advanced through the site of thrombosed segment (e.g. Radiofocus™, Terumo medical, Tokyo, Japan or ZIP wire™, Boston Scientific, MA) (Figure 4).

Figure 2: Extension of the thrombus to popliteal artery.

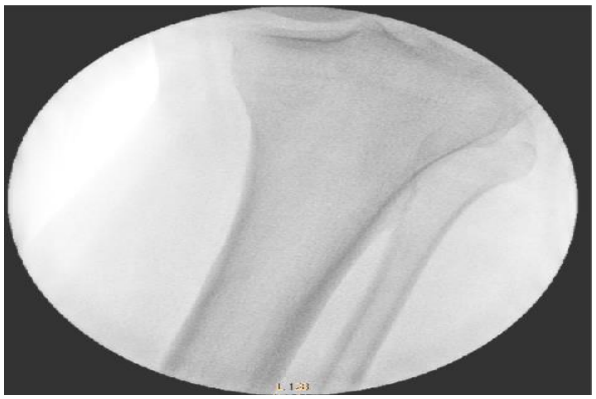

Figure 3: No distal run-off flow through tibial vessels.

Figure 4: Wire traversed.

The multi- holes 5F thrombolysis catheter was advanced and its infusion length was positioned through the proximal end of occlusion (Fountain Infusion Catheter™, Merit Medical Systems, Inc.) (Figure 5).

Figure 5: Positioning of multi-hole thrombolytic catheter.

Its tip occlusion wire was positioned under fluoroscopy. The thrombolytic agent, Actilyse™ (Boehringer Ingelheim, Ingelheim, Germany) was prepared using its solvent forming a concentration of 1mg/mL.

The method of infusion used was intra-thrombus bolus administration firstly of a mean dose of 5-10 ml TPA followed by continuous infusion of 1mg/h. The sheath and catheter were looped in the groin, draped and fixed in position. 500 IU/hr UFH was infused through the sheath to guard against peri-catheter thrombosis. Patients were monitored thoroughly in ICU or intermediate care unit especially to the ischemic manifestations of the limb, coagulation profile e.g. PTT to avoid bleeding complications.

Figure 6: Complete lysis of the thrombus.

Follow up angiography was conducted according to the clinical course. If there was initial clinical improvement, the 1st follow up angiography was conducted usually after 12 hours and then according to clinical course. The value of follow up angiographies was to detect the progress of thrombolysis, restoration of flow and for catheter repositioning (Figure 6,7). Any underlying lesion detected was managed by balloon angioplasty.

Figure 7: Restoration of flow through popliteal and tibial vessels.

Follow-up was conducted in vascular surgery outpatient clinic weekly within the first month then at 3 and 6 months regarding regaining pulse, clinical improvement and ABI measurements.

Also, technical success or failure, clinical improvement, major or minor bleeding were recorded. Post-procedural medications with dual antiplatelet therapy in the form of salicylates 75 mg and Clopidogrel 75mg as a maintenance daily dose continued for at least 3 months.

Study endpoints: Thrombolysis was terminated if there was angiographic restoration of distal flow or appearance of distal pulses, no progress of thrombolysis procedure confirmed by two successive follow up angiographies or occurrence of major complication (major bleeding or deterioration of limb ischemia). Major bleeding was considered when (i) patient need for blood transfusion of ≥ two units, (ii) surgical intervention to stop hemorrhage, (iii) extended or unexpected hospitalization.

Technical success was defined as restoration of adequate flow and dissolution of at least 95% of the occlusion while clinical success was gained by relief of acute ischemic symptoms or reduction of the level of subsequent surgical intervention as recommended by others.[9,6]

RESULTS

This study was performed on 18 patients with acute thrombotic lower limb ischemia (Rutherford II-a). Major risk factors were diabetes and smoking as their incidence were 66% and 56% respectively. The common site of thrombosis was SFA artery. All demographic data and patients' criteria were summarized in Table 1.

Table 1: Demographic data and patient's criteria.

Demographic data	
Age /Y	49 (45-69)
Males/Females	13/5
Risk factors	
DM	12 (66 %)
Smoking	10 (56 %)
Ischemic heart disease	8 (44 %)
Stroke	3 (17 %)
Duration of thrombolysis procedure/h	25 (20- 37)
Site of occlusion	
SFA	44.4%
Popliteal artery	11.1 %
Iliac artery	11.1 %
Combined	33.4 %
Technical success	83%
Limb salvage	77.7%
Complications	
Minor bleeding	3 (16.6%)
Major bleeding	0%
Amputation	2 (11%)
Death	3 (16.6%)

Technical success was achieved in 15 patients (83%). Complementary revascularization was performed in 5/15 patients (33.3 %) by balloon angioplasty to the underlying lesion. Limb salvage rate at 6 months follow up was (77.7%). Failure of thrombolysis which proved by lack of progress in thrombolysis procedure occurred in 3 limbs (16.6%). All failed procedures were in patients with thrombosed distal femoro-popliteal segment. Inability to traverse the guidewire through the lesion was a prognostic criterion of failure. One patient was treated by femora-popliteal bypass while the other two limbs were ended by amputation due to unsuitable distal run-off vessels for revascularization.

Regarding complications, bleeding (local groin hematoma or minimal retroperitoneal) occurred in 3 patients (16.6 %) and were treated conservatively. No major bleeding was recorded. Amputation had performed in two patients (11%) while mortality rate within 6 months was 16.6 % (3 patients). Two patients of them died after successful thrombolysis due to associated coexisting morbidities and the other one died after limb amputation.

DISCUSSION

The last decades had witnessed an evolution to minimally invasive techniques in thrombotic ischemia e.g. CDT which is considered a life and limb-saving procedure for selected patients.[10] It is intended to deliver maximum volume of thrombolytic agent to the thrombus while simultaneously reducing systemic thrombolytic spill.[11] Naidoo and his colleagues reported that CDT was indicated in patients with Rutherford II-a ischaemia while patients with Rutherford II-b ischaemia were excluded because of advanced ischaemia that require immediate surgical intervention.[11] Kasirajan reported that advances in percutaneous mechanical thrombectomy (PMT) techniques provided the feasibility even in selected cases with Rutherford II-b e.g. poor surgical risk patients, especially in vascular centers where these facilities were available.[10,12] Rutherford II-a and Rutherford II-b criteria were shown in Table 2.

Table 2: Severity of Acute Leg Ischemia.[12]

	Category	Description	Capillary return	Muscle paralysis	Sensory loss	Doppler signals	
						Arterial	Venous
I	Viable	Not immediately threatened	Intact	None	None	Audible	Audible
IIa	Threatened	Salvageable if treated	Intact/slow	None	Partial	Inaudible	Audible
IIb	Threatened	Salvageable if treated as emergency	Slow/absent	Partial	Partial	Inaudible	Audible
III	Irreversible	Primary amputation frequently required	Absent	Complete	Complete	Inaudible	Inaudible

Three randomized multicentre trials compared thrombolysis with surgery; Rochester study, Surgery versus Thrombolysis for Ischemic Lower Extremity (STILE) trial, and the thrombolysis or peripheral arterial surgery (TOPAS) trial.[13-15] The consensus concluded that thrombolysis should be considered first-line treatment for acute thrombotic ischemia when: (1) Symptoms of limb ischemia are less than 2 weeks, (2) No absolute contraindications for thrombolysis, and (3) The predicted time to re-establish antegrade flow is short enough to save limb. The commonly used thrombolytic agents are plasminogen activators, they activate plasminogen, convert plasminogen to plasmin which in turn breaks down the fibrin and fibrinogen within the clot into fibrinogen degradation products. All available drugs have variable degrees of fibrin specificity. Streptokinase (SK) and urokinase (UK) are non-fibrin-specific plasminogen activators while tissue plasminogen activators (tPAs) are fibrin-specific agents. Higher fibrin specificity of TPA was the reason of less systemic bleeding complications; however, large trials had shown no significant difference in bleeding rates.[7]

Swischuk et al, had shown the appropriate doses of (TPA) whatever weight- based or non-weight- based and they summerized the appropriate dose from 0.02-0.1mg/kg/h.[16] whereas non-weight-based doses generally ranged from 0.25-1.0mg/h, even though higher doses were reported. However, there were no significant differences between the two groups regarding limb salvage or complication rates. Harry had reported in his series that guide wire traverse provided an information about the consistency of the clot and then prognosis of successful thrombolysis.[8] If the guide wire traverses the occluded segment easily, the clot responds to thrombolysis. If the occlusion cannot be traversed, an end hole catheter can be positioned proximally to the thrombus and thrombolysis got started. Few hours after, the proximal fibrin plug will be assessed for softening and then the guide wire can be advanced through the occlusion. On the contrary, if the guide wire cannot be advanced, one should terminate the thrombolysis procedure.

There are multiple methods for thrombolytic agent delivery: continuous infusion, lacing (blousing), pulse spray, graded infusion, and stepwise infusion.[17] Kessel and his colleagues reported that there were no significant differences in amputation-free survival between these methods.[18] Some reports, showed an increased rate of bleeding with high dose bolus technique compared with continuous infusion whereas others do not.[12] Lacing technique refers to infusion of large concentrated dose of thrombolytic agent along the length of the thrombus aiming for saturating the thrombus with the plasminogen activator before starting infusion.[19] Semba et al, reported that the Society of Interventional Radiologists (SIR) advisory panel recommended a maximum dose of 2mg/h for a maximum total infusion of 40mg.[20] Finally, it has been shown that a dose more than 1 mg/h will not improve efficacy but increases bleeding complications.

Heparin infusion is to prevent immediate re-thrombosis of treated vessels and to prevent peri-catheter thrombosis. Infusion rate of 200-500IU /h to raise PTT to 1.25-1.5-fold of normal value is recommended.[8] In this study, the procedure started with dose of 5-10mg to 'lace' the thrombus and continued by infusion dose of 1 mg/h. Regarding the heparin infusion, its dose was 500 units / hour into the sheath to prevent peri- catheter thrombosis as recommended in other series.[8,20] The need for adjunctive techniques for treatment of the underlying lesion predicted the long-term patency and limb salvage rates. Hanover et al, found that patients requiring thrombolytic therapy only without need to endovascular or surgical intervention had higher primary patency rates (95.2%, 88.4% at 1,12 month) respectively and (100%) one-year limb salvage rate compared with those who necessitated adjunctive endovascular or surgical treatments.[21] Complementary balloon angioplasty was performed in (33.3%) of cases in this series. These results were matched with Cina et al, who reported that 38% of cases required some form of surgical or endovascular intervention.[19] In this study, Technical success was 83 % which was quietly similar with other different series used the same thrombolytic agent; Vignali et al., Cina et al, which was 88%, 79.7 % respectively.[19,22]

In this series, we were not capable of monitoring patients by serum fibrinogen level during thrombolysis because it was unavailable in our hospital. There was a controversy in association of low fibrinogen levels and bleeding complications.[7] Fibrinogen levels of <1.2g/L were a risk factor for bleeding complications as in the STILE trial, which reported that patients with bleeding complications had lower fibrinogen levels and prolonged prothrombin and activated partial thromboplastin times. Ward et al found FDP elevated in 3/4 patients with major hemorrhagic complications secondary to r-TPA.[23,24] Also, Cina et al, had suggested that bleeding risk correlates with the level of fibrin degradation products (FDP) rather than fibrinogen.[19] Ouriel K et al, had reported that FDP may act as an anti-platelet agent and as an anticoagulant producing an inhibitory effect on fibrin polymerization.[25]

Minor bleeding in this series either local groin hematoma or minimal retroperitoneal hematomas occurred in 3 patients (16.6%). Nearly similar incidences were obtained by Vignali et al. and, Ouriel et al, who reported 12% and 11 % respectively.[15,22] In STILE trial, amputation rate was higher in surgical group than in fibrinolytic group for ischemia less than14 days duration and it was lower in those with more than 2 weeks.[19] Also, Camerota and White JV reported in their thesis that amputation rate was increasing seriously by the duration interval between onset of symptoms and initiation of thrombolytic therapy.[26] They concluded that amputation rates were 6% if thrombolytic therapy was initiated within 12 hours of onset of acute symptoms, 12% if initiated between13-24 hours, and 20% if initiated after 24 hours.

Also, Nilesh et al, reported that lower amputation and mortality rates occurred with ischemia less than 2 weeks.[7] Amputation had performed in (11%) in this study while it was reported 8 % in series of Cina et al.[19] Mortality rate within 6 months was 16.6 % (3 patients) in this study while it was 7 % with others.[19] The difference can be attributed by the small number of cases in this study. Mehta and his colleagues reported the use of post-thrombolysis medications as a prophylaxis by aspirin and clopidogrel daily for 6 weeks to prevent recurrent thromboses.[27]

CONCLUSION

With proper patient's selection, CDT should be considered the first-line treatment for patients with early acute thrombotic limb ischemia.

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