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ORIGINAL ARTICLE

INTRA ARTERIAL THROMBOLYTIC THERAPY FOR ACUTE THROMBOTIC ISCHEMIA.

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Aim: *To evaluate the early and late results of thrombolysis in acute thrombotic ischaemia and graft occlusion.*
Patients and methods: *In a prospective randomized study 40 patients with thrombotic ishaemia were divided into two groups. Group A :20 patients underwent thrombolytic therapy. Group B : 20 patients underwent surgical reconstruction .*
Results: *Group A: Primary success in 17 patients (85%).*
Failure of thrombolysis in 3 patients (15%) Primary patency rate 85%. No mortality occurred during follow up.
Group B: Primary success rate was 75 %(15 patients). In 3 patients with acute thrombosis amputation was performed, one due to secondary hemorrhage and ligation of the graft .and the other two were due to graft failure and gangrene during the first month postoperatively. Mortality occurred in 2 patients (10%)
Conclusions: *Thrombolysis as compared with immediate surgery reduces the number of open procedures required for acute ischemia of the lower limb & allows some patients to avoid surgical intervention.*

Keywords: *Thrombolysis, Urokinase, Acute Ischaemia.*

INTRODUCTION

The most effective means of dissolving clot is activation of plasminogen bound to fibrin within the matrix of the clot ,this is based on catheter delivery of plasminogen activator directly into the thrombus.The fibrin bound to the plasminogen molecule within the thrombus makes that plasminogen molecule particularly susceptible to activation by plasminogen activator. If delivered into the thrombus the plasminogen activator is protected from neutralization by circulating plasminogen activator inhibitor.(1)

Mc Nichol and colleagues(2) fist attempted local delivery of fibrinolytic agent for arterial thrombosis in 1963. Dotter and colleagues(3) extended and promoted catheter directed intra-arterial delivery of thrombolytic agents .

Van Breda, et al(4) demonstrated that Urokinase was safer and more effective than Streptokinase as a lytic agent.

Mc Namara & Bomberger(5) reported better results of CDT (CDT) for patients with acute lower limb ischemia due to arterial emboli than graft thrombosis.

The primary therapeutic objective of CDT is to dissolve the occluding thrombus restoring the perfusion and allowing for correction of the underlying lesions without the occurrence of severe local or systemic complications.(6)

The standard treatment of acute arterial occlusion is open surgery, but the bad general condition and the comorbidity of many medical conditions leading to a high rate of perioperative morbidity & mortality; so intra arterial thrombolysis is considered as an alternative to open surgery in such cases with reported high mortality rate 10%-30%(7) Important additional goals of thrombolytic therapy are to convert an urgent procedure into an elective one, gain patency of an occluded but non diseased inflow source for subsequent bypass, convert a major vascular

reconstruction into a limited procedure, & reduce the level of amputation in patients with incomplete success (limb salvage).[8]

Aim: To evaluate the early and late results of thrombolysis in acute thrombotic ischaemia and graft occlusion.

PATIENT & METHODS

In this study 20 patients with acute thrombotic ischemia were included in group A after fulfilling the inclusion and exclusion criteria for thrombolytic therapy. Other 20 patients with acute thrombotic ischemia were included in group B for operative reconstruction.

In a prospective randomized study to evaluate efficacy and safety of intra-arterial CDT for acute limb ischemia of less than 14 days duration using urokinase compared to standard operative revascularization.

Inclusion criteria: Patients with non-embolic acute limb ischaemia following arteriographic documentation of obstruction of a native artery or bypass graft with non-embolic limb ischemia, which may be due to atherosclerosis (acute thrombosis on top of chronic ischemia, thrombosed popliteal aneurysm and thrombosed bypass graft either autogenous or prosthetic grafts).

Exclusion criteria includes: patients with acute embolic ischemia, and patients with contraindication to thrombolysis as recent stroke, intracranial trauma or surgery, active bleeding, pregnancy and recent operations (within 10 days of surgery).

Technique: Planning for intra-arterial thrombolytic therapy should start before performing the angiography. The approach is usually contra lateral femoral artery (retrograde) if femoral artery pulse is not felt or by ante grade ipsilateral direct femoral method if the lesion is below the common femoral artery.

An attempt at guide wire passage of the occlusion, if successful thrombolytic therapy is possible but if the guide wire cannot be passed through the lesion, primary operative reconstruction is indicated.

In this study high dose of urokinase was used as thrombolytic agent . The initial dose is 500,000unit bolus , followed by 4000 unit per minute until recanalization is achieved, the dose could be then reduced to 1000-2000 units/minute. Broad spectrum antibiotics are given intravenously at time of the procedure.

Complete coagulation profile and blood studies are performed before and during treatment. Intra-arterial catheters (Mewissin or multiple side holes catheter) were used to infuse intrathrombus directly or regional infusion is started above the thrombus for some time to open the track in the thrombus through which the arterial catheter could be advanced to infuse intrathrombus.

Pericatheter thrombosis could be prevented by heparin infusion to reach partial thromboplastin time of not more than twice the normal. All patients are treated in intensive care unit, and remained at absolute bed rest. Angiography is performed to follow the therapeutic response and guide the poisoning of the catheter. The initial 2 to 4 hours of infusion is generally performed in the radiology suite, catheters are then advanced directly into the thrombus. In cases with multisegment lesions infusion of the thrombolytic agent is performed through a coaxial system, splitting the dose to be relatively higher to the distal occlusion.

During the process of infusion monitoring of prothrombin time, partial thromboplastin time and fibrin degradation products, if the fibrinogen level drops below 100 mg dl, we slow or stop the infusion and in cases with serious bleeding, fresh frozen plasma or cryoprecipitate could be given.

The infusion is stopped after complete recanalization of the native artery or the graft, or if no more progress occurred on the follow up angiography on the next day, or after 48 hours from the start of lytic therapy, and if there is deterioration of the ischemic limb.

After successful lysis, identification of the underlying cause of occlusion and its correction should start immediately using the interventional techniques.

Informed consent for participation in the study was obtained.

Statistical Analysis: the data was statistically analyzed by Kruskal-Wallis and media tests were used to find a significant difference . A probability value (P) of less than0.05

(< 0.05) was considered to be a significant value.

Follow Up: The patients were followed up clinically and by means of non invasive measures for 2 years , recording the outcome of treatment modality , complications, and the patency rates.

RESULTS

Demographic data of the two groups is shown in Table 1.

There was no statistical significance between the demographic data of the two groups.

In group (A) Successful intrathrombus infusion from the

start was possible in 13 patients (65%) while in 4 patients (20%) regional infusion started at first to open a track in the thrombus followed by advancing the catheter intrathrombus .

As regards the results of management of group A: Primary success in 17 patients (85%) (Examples of cases are shown in Figs. 1-5). Failure of thrombolysis in 3 patients (15%) (Example is shown in Fig. 6)

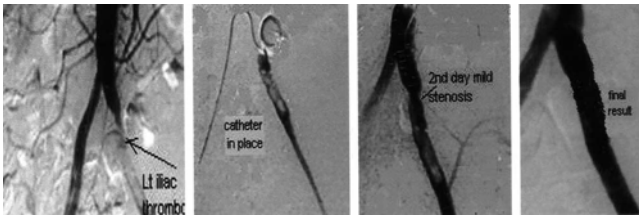

Fig 1. Left Iliac Thrombolytic Therapy

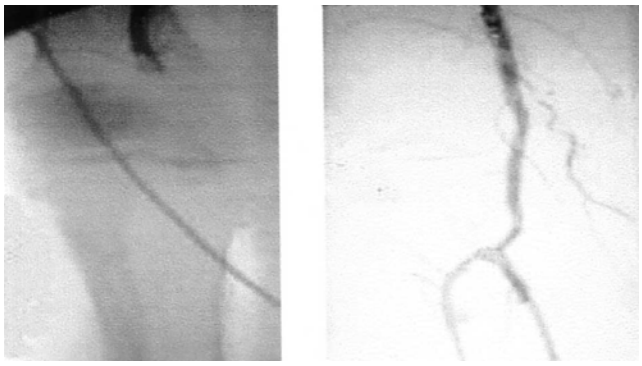

Fig 2. Popliteal Thrombolysis

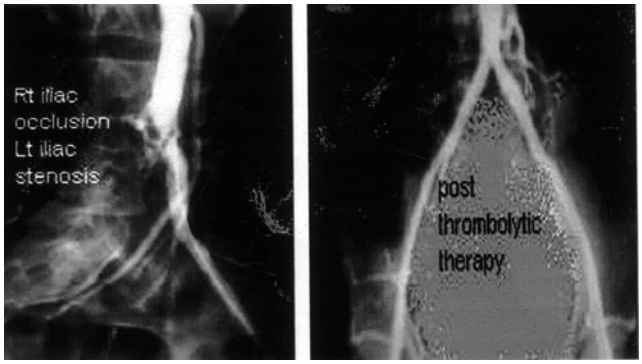

Fig 3. Iliac thrombolytic therapy & angioplasty

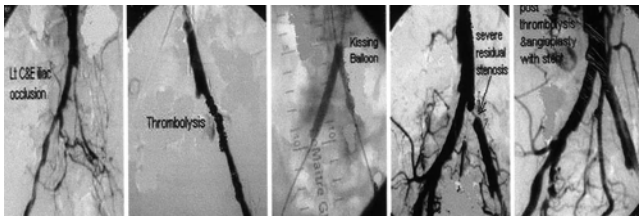

Fig 4. Thrombolytic followed by Angioplasty and Stenting

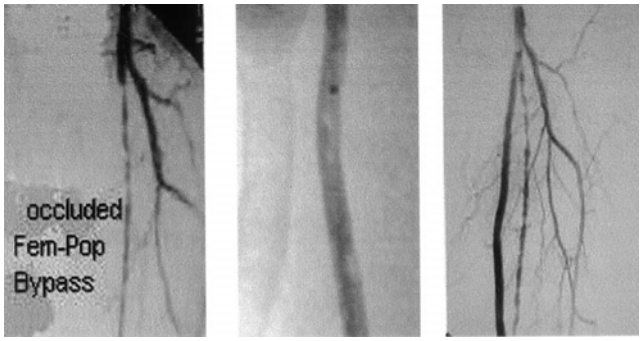

Fig 5. Thrombolysis of occluded bypass

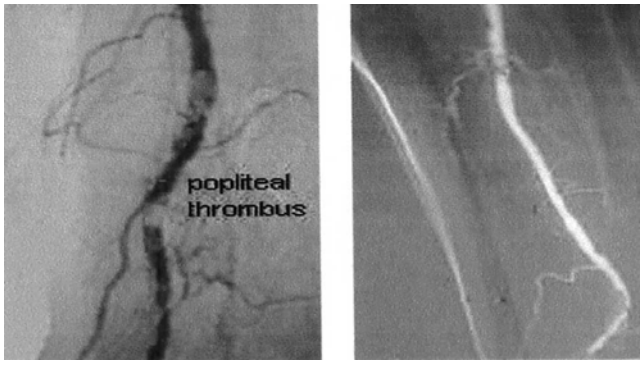

Fig 6. Popliteal thrombolysis with residual stenosis (Terminated)

Primary patency rate 85%. In 3 patients' complementary angioplasty and stent was performed to maintain limb patency (Examples of cases are shown in Figs. 3,4), while in 3 patients femoropopliteal grafts were indicated following thrombolysis. Infusion time ranged from 8 to 48 hrs (mean 12.2±5.3 hrs.) The outcome of management according to the aetiology in group A is shown in Table 2

No mortality occurred during the period of follow up (2 years) in group A.

In 3 patients (15%) failure of thrombolysis necessitating conversion to operative management in 2 patients (10%).

Femorodistal bypass grafts were performed and the procedure was successful in one patient only, while in the 2nd patient above knee amputation was done on the 5th day postoperatively in the 3rd patient and with failure of thrombolysis, primary amputation was indicated from the start after exploration that revealed occluded distal vessels.

As regards the complication of treatment in group A: one patient (5%) with thrombosed prosthetic femoropopliteal graft developed distal emboli that required catheter advancement more distally and continued infusion with a higher dose (5000/unit/min) for one hour where this patient developed mild bleeding ,and later on developed small false aneurysm that could be managed conservatively.

In other 2 patients (10%), low grade fever developed that was treated with oral antipyretic drugs. The operative revascularization in group B: according to the aetiology is shown in Table 3. Complications in group B are shown in Table 4.

In group B the primary success rate was 75% (15 patients)

In 3 patients with acute thrombosis amputation was performed ,one due to secondary hemorrhage and ligation of the graft .and the other two were due to graft failure and gangrene during the first month postoperatively .

In 1 patient with occluded graft and insertion of a new graft reocclusion and gangrene development. In 1 patient with thrombosed aneurysm , occlusion of femoro-posterior tibial graft occurred postoperatively.

As regards complications of treatment in group B: Wound infection: gross wound infection In 3 patients (15%).Secondary hemorrhage in 1 patient (5 %).Wound hematoma in 2 patients (10%).Primary graft failure in 5 patients (25%). Mortality in 2 patients (10%)

One with above knee amputation (AKA) after failure of femorodistal graft for occluded graft .And one with failed graft after thrombosed popliteal aneurysm, both patients had myocardial infarction.

In our study the primary success rate in the thrombolytic group (group A) was 85% versus 75% in the surgical group (group B) ($P<0.05$) which is statistically significant.

One year limb survival was 80 % in group A versus 65% in group B ($P<0.05$) which is statistically significant.

Two year limb survival was 65 % in group A versus 60% in group B ($P=0.85$) which is statistically insignificant.

Table 1. Demographic data of the two groups.

	Group A **Thrombolytic therapy 20 patients**	**Group B** **operative 20 patients**
Mean age (year)	51.55±9.2	50.49±9.5
Gender: male	18 (90%)	17 (85%)
female	2 (10%)	3 (15%)
Risk factors		
Diabetes mellitus	14(70%)	13 (65%)
Ischaemic heart disease	13 (65%)	11 (55%)
Cause of acute ischemia		
Acute thrombosis	12 (60%)	15 (70%)
Graft occlusion:	6	3
Saphenous vein	2 (10%)	2 (10%)
Prosthetic graft	4 (20%)	1 (5%)
Throm.popliteal aneurysm	2 (10%)	2 (10%)

Table 2. Outcome of management according to the aetiology in group A.

	Primary success	Distal emboli	Bleeding	False aneurysm	Low grade fever	One Year limb survival	2 year limb survival
Acute thrombosis 12 patients	10 patients (83%)	--	1 (10%)	--		9 patients (75%)	9 (75%)
Graft occlusion 6	5 patients						
Saphenous 2	2 100%					2 (100%)	1(50%)
Prosthetic 4	3 75%	1(25%)	1 (25%)	1 (25%)	1 (25%)	3 (75%)	2 (50%0
Thrombosed popliteal Aneurysm 2	2 patients 100%	--		--	1 (50%)	2 (100%)	1 (50%)

Table 3. The operative revascularization in group B: according to the aetiology.

Group B	Operation	Success
Acute thrombosis	10 Femoro-popliteal graft	9
15 patients	5 Femoro-distal graft	3
Graft occlusion 3		
Saphenous	Saphenous vein below the knee	1
2 patients	Reinforced PTFE graft	0
prosthetic	Thrombectomy and bridge graft from the old graft to lower popliteal artery	1
1 patient		
Thrombosed popliteal aneurysm	Exclusion and femoro- tibial bypass graft	1
2 patients		

Table 4. Complications in group B.

Acute thrombosis 15	Graft failure	Wound infection	secondary hemorrhage	Wound hematoma	One year limb salvage	Two year L salvage
	3	**2**	**1**	**1**	**11(73%)**	**10(66%)**
Graft occlusion						
Saphenous 2	--			1	1(50%)	1 (50%)
Prosthetic 1	1	1			0	0
Thrombosed popliteal aneurysm 2	1	--	--	1	1(50%)	1(50%)

DISCUSSION

Thrombosis is one of the two main causes of peripheral arterial occlusion. Surgical treatment of acute limb ischemia has a 30-day mortality rate of 15-25%.

Intra-arterial thrombolysis is a well accepted technique, it may offer a definitive treatment without requiring major surgery in patients with acute occlusion of native leg arteries or bypass graft.[9]

CDT has become an important part of treatment in patients with acute thrombotic ischemia and graft occlusion in primary successful recanalization and survival rate due to the ability of thrombolytic agents to clear thrombus from small arteries which are not accessible for a balloon catheter in open surgeries. It unmasks the lesion responsible for occlusion and allows a direct and less invasive treatment.[10]

In this study criteria for choosing patients with acute thrombotic ischemia , graft occlusion and thrombosed popliteal aneurysm, with ischemia duration less than 14 days to allow better lysis of the relatively recent clot depending on the criterion of TASC working group 2000[11]

The used thrombolytic agent in this study was urokinase with initial dose 500000 unit bolus followed by 4000 unit

per minute until recanlization is achieved, the dose could be then reduced to 100-2000 unit/min.

Urokinase is a direct activator capable of inhibiting fibrinolysis without forming an activator complex, it cleans plasminogen by first order reaction kinetics to plasmin. Its direct mechanism of action allows for a better dose response relationship compared to streptokinase. Activation of plasminogen by urokinase occurs through proteolysis of its substrate, on intravenous administration it is rapidly removed from circulation via hepatic clearance. Its half life is 14 min.[4]

The primary therapeutic aim of CDT is to dissolve the occluding thrombus restoring the perfusion to the affected limb and allowing definitive correction of the underlying lesion.

Other important goals of thrombolytic therapy are:

1-Conversion of an urgent surgery to an elective one.

2-Gaining the patency of an occluded but non-diseased inflow source for subsequent bypass.

3-Lysis of thrombi in the distal vasculature restoring patency of outflow tract.

4-Converting a major vascular reconstruction to a limited procedure.

5-Preventing arterial intimal injury from balloon catheter thrombectomy.

6-Reducing the level of amputation in incomplete lysis as a limb salvage .[10]

Van Bred et al., reported that urokinase was found to be safer and more effective than streptokinase as a thrombolytic agent.[4] Mc Namara and Bomberger, 1986, reported good results of CDT using high dose urokinase in patients with acute lower limb ischemia.[5] Sullivan et al, 1991 demonstrated good results for thrombolytic therapy in occluded graft (85-91%) suprainguinal (59-66%) infrainguinal, however other authors have failed to demonstrate the same degree of effectiveness of CDT for graft occlusion reporting one year patency rate of 30% to 40%.[13,14]

In our study the primary patency for the thrombolytic therapy was 85%.

In other randomized trials the efficacy and safety of thrombolytic therapy have been studied versus surgical revascularization.[15] Out of 114 patients enrolled in this study, 70% of CDT patients achieved successful management, the cumulative limb salvage was similar for the two treatment groups(82% at 12 months), however, the cumulative survival rate was significantly improved in patients randomized to thrombolysis(84%vs 58%) at 12 month which was statistically significant(p=0.01).

The same observation was reported by Comerota etal., in 1993.[16] in the first large prospective multicenter trial (Surgery vs. Thrombolysis for the Ischemic Lower Extremity) (STILE) when the outcome was analyzed by duration of the ischemia it became apparent that patient with ischemia < 14 days had a significantly better outcome when treated with catheter directed thrombolysis compared to patients randomized to operative revascularization. Comerota et al., in 1996[8] studied the results of patients with occluded lower limb bypass grafts and found that the average duration of graft occlusion was 34 days so 34% randomized to lysis failed to have the catheter properly positioned and therefore reverted to surgical revascularization but after successful catheter placement , patency was restored to 84%, and in the lytic group 42% had a major reduction in their planned operations. Weaver et al., 1996[17] analyzed the results obtained in 237 STILE patients with native artery occlusion and found that 78% of patients could have the catheter properly positioned and lytic agent infused leading to a reduction in the surgical procedure in 56% of patients. In this study failure of thrombolysis in 15% of patients necessitating conversion to operative management in 2 patients (10%) femorodistal bypass graft were performed and in the 3rd patient amputation was indicated after exploration of distal vessels which were occluded.

Ouriel et al., in 1998[18] reported that analysis of urokinase versus operative revascularization as the initial treatment for acute lower extremity arterial or graft occlusion (TOPASII) (Thrombolysis Or Peripheral Arterial Surgery) trial ,and found that amputation free survival rate in urokinase group was 72% at 6 months and 65% after one year as compared to 75% and 70% in the surgical group, but with 43% reduction in the operative procedures in the lytic group.

Despite the apparently different outcomes between the STILE and TOPAS II trials, there may be more similarities of the two trial are tabulated according to the endpoints of TOPAS II trial which is the amputation free survival because most patients do not die and most do not lose a limb.

In our study the primary success rate in the thrombolytic group (group A) was 85% versus 75% in the surgical group (group B) (P<0.05) which is statistically significant.

One year limb survival was 80 % in group A versus 65% in group B (P<0.05) which is statistically significant.

Two year limb survival was 65 % in group A versus 60% in group B (P=0.85) which is statistically insignificant.

In group A no mortality was recorded during a period of 2 year follow up, while 2 patients died in group B (10%), one with above knee amputation after failure of femorodistal bypass graft for occluded graft and one after failure of graft for thrombosed popliteal aneurysm , both patients had myocardial infarction.

As regards the complications of thrombolytic therapy in this study, no allergic reaction was recorded in this study with urokinase as thrombolytic agent while in other studies using streptokinase as thrombolytic agent allergic reactions were observed in up to 30% of the patients as bacteria are the source of streptokinase, so foreign protein from the cell wall of the bacteria accounts for the allergic and pyretic reactions.[16]

Distal embolization occurred in one patient with occluded prosthetic graft (5%), no distal embolization occurred in patients with acute thrombosis, this observation was recorded by other studies[7,8] in patients with distal emboli the catheter then advanced more distally and continued infusion was successful to lyse distal emboli.

Bleeding was recorded in 10% in patients of group A while only in 5% group B which is statistically insignificant.

Bleeding usually occurs as a result of the active lytic state following dissolution of the thrombus but can also be due to the induced coagulopathy caused by the lytic agent. In this study the incidence of bleeding was less than that recorded in other thrombolytic therapy studies with only mild bleeding and no attacks of sever bleeding or intracerebral bleeding. The incidence of bleeding complication may reach up to 30% (de Bono, & More 1993)[18] which could be reduced by minimizing the trauma of invasive procedures & proper planning of appropriate catheter or sheath placement with minimal additional trauma.. Also laboratory monitoring of fibrinogen was linked to the incidence of serious bleeding complications in patients with prolonged catheter cannulation , hemostatically ineffective fibrinogen, low fibrinogen concentrations & platelets[20,21]

In this study, wound hematoma occurred in 10% of patients in the surgical group B.

Technical complications in this study : false aneurysm at the puncture site occurred in 5% of patients (one patient with prosthetic graft occlusion). It was found also in other studies that patients with prosthetic graft are liable to extravasation of contrast material & late development of false aneurysms[22,23]

In conclusion Thrombolysis as compared with immediate surgery reduces the number of open procedures required for acute ischemia of the lower limb & allows some patients to avoid surgical intervention with its significant rate of mortality & with amputation free rate comparable to the operative procedure so thrombolytic therapy can offer patients definitive treatment with significantly less accompanying trauma & complications than major surgical procedures.

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