Summary
In the UK, approximately 5000 patients present annually with acute lower limb ischaemia. The aetiology is usually thrombo-embolic disease, other causes include aortic dissection and arterial trauma. Over the past two decades thrombosis has replaced embolism as the principal cause of acute ischaemia, and now accounts for approximately 59% of cases. As a consequence, intra-arterial thrombolysis is being increasingly used as first-line treatment for this condition.

Keywords: intra-arterial thrombolysis, acute arterial occlusion

Lower limb intra-arterial thrombolysis

Jonathan Golledge, Robert B Galland

Lower limb thrombo-embolism can present in a number of ways.¹ These include acute intermittent claudication, acute rest pain with evidence of critical ischaemia, or as an acutely white paralysed limb. The latter is less common following thrombosis due to the presence of collateral inflow. Once thrombo-embolic occlusion has been diagnosed the patient should be anti-coagulated with heparin. Thrombosis is suggested by a history of pre-existing claudication. Pulses may be absent in the other leg. A patient with atrial fibrillation or who has recently had a myocardial infarction may have embolic disease. The pulses in the other leg are often normal (table 1). If there is an embolic cause, embolectomy is undertaken, although in the absence of sensory motor disturbance thrombolysis has been used successfully in these circumstances. If thrombosis is suspected and the limb is viable then an urgent angiogram should be obtained. An intravenous digital subtraction angiogram may give preliminary information, however, intra-arterial studies give more precise information.

In 1933, Tillett and Garner found that cell-free filtrates of broth cultures of streptococci rapidly liquefied human fibrin clot. The active agent was purified and became known as streptokinase.² In the 1950s it was used in clinical trials. Johnson and McCarty induced thrombosis in the peripheral veins of volunteers by chemical irritation with sodium morrhuate. They were able to lyse five of seven thromboses by giving an initial loading dose followed by continuous infusion of intravenous streptokinase.³

The use of intravenous streptokinase to treat intra-arterial thrombosis has never become popular. A recent review of 390 reported cases revealed that lysis was only achieved in 39%.⁴ The complication rates were high, including death (5%), haemorrhage (9%), stroke (2%) and distal embolisation (7%).

In 1962 Cotton *et al* used intra-arterial streptokinase in the treatment of post-embolectomy thrombosis.⁵ The common femoral artery was exposed, a loading dose of streptokinase given directly into the artery and then a catheter was passed down the artery. A continuous infusion of streptokinase achieved lysis in 24 hours. In 1974 Dotter *et al* described the use of a percutaneous Seldinger technique to introduce intra-arterial catheters and deliver streptokinase directly into the thrombus.⁶ The dose of streptokinase used was one hundredth of that required intravenously. Thrombolysis was successful in seven of the 17 patients. However, it was not until the 1980s that the results of large series of patients treated by intra-arterial thrombolysis were published (table 2).

Thrombolytic agents

The three main agents used are streptokinase, urokinase and recombinant tissue plasminogen activator (t-PA) (see table 3). They act by activating plasmin, which breaks down fibrin. Other agents which have been tested include acylated plasminogen–streptokinase activator complex. Streptokinase is relatively cheap but can be associated with allergic reactions. It is usually given as an infusion of 5–10 000 units/h until lysis is complete or no further lysis is taking place.

Urokinase, an endogenous plasminogen activator, originally isolated from urine, has been extensively used in the US. It costs up to six times more than streptokinase.²¹ It has principally found favour as a high-dose infusion of 4000

Table 1 Comparison of thrombosis and embolism

	Thrombosis	Embolism
Incidence	60%	40%
Presentation	Acute on chronic ischaemia	Acute white limb
Past history	Intermittent claudication	Atrial fibrillation, recent myocardial infarction
Examination	Chronic ischaemia may be present in other limb	Pulses may be present in other limb
Treatment	Thrombolysis	Embolectomy

Department of Vascular Surgery, Royal Berkshire Hospital, Reading, Berkshire, UK
J Golledge
RB Galland

Correspondence to Mr J Golledge, 20 Hill Crest Close, Thornhill, Cardiff, CF4 9ER, UK

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Table 2 Typical major reported series of thrombolysis for lower limb acute thrombo-embolic disease

Ref	Years of study	n	Treatment	Early success (n (%))	Early re-occlusion (n (%))	Late patency	Major complications (%)		
							Death	Haemorrhage	CVA
7	1982–84	83	sk	55 (66)	–	–	–	10 (12)	1 (1)
8	1981–85	100	uk	77 (77)	32 (41)	–	3 (3)	5 (5)	–
9	1983–85	102	sk	72 (71)	–	–	11 (11)	3 (3)	–
10	1985	136	sk/uk	107 (78)	10 (10)	81% at 2 years	–	5 (4)	–
	1980–85	564	sk	313 (55)	96 (25)	59% at 5 years	9 (2)	8 (1)	2 (1)
12	1982–87	72	sk	52 (72)	–	–	5 (7)	4 (6)	–
13	1985–88	59	sk/tpa	40 (68)	–	–	7 (12)	4 (7)	–
14	1989	202	sk	165 (82)	–	–	29 (14)	5 (3)	2 (1)
15	1982–86	134	sk	66 (49)	12 (18)	63% at 5 years	5 (4)	–	–
16	1985–88	71	uk	41 (58)	–	20% (p)/55% (a) at 1 year	1 (1)	11 (15)	1 (1)
						70% at 3 years	53 at 30 ds	–	3 (2)
17	1985–89	129	sk/tpa	63 (49)	12 (19)	–	2 (2)	4 (4)	1 (1)
18	1988–90	100	sk/tpa	75 (75)	16 (21)	–	2 (2)	9 (11)	–
19	1981–91	84	uk	50 (60)	–	–	5 (4)	10 (8)	1 (1)
20	1986–93	134	uk	71 (53)	15 (21)	–	79 (5)	78 (5)	11(1)
Total		1970		1247 (63)	162 (12)	–			

SK = streptokinase, uk = urokinase, tpa = tissue plasminogen activator, p = prosthetic graft, a = native artery thrombosis.

Table 3 Thrombolytic agents

	Streptokinase	Urokinase	t-PA
Source	haemolytic streptococci	urine	recombinant DNA technology
Price	cheap	expensive	expensive
Dose	5–10 000 U/h	4000 U/min	5 mg boluses, 0.5 mg/h
Use	popular in UK	USA	increasingly popular in UK
Speed of action	slow	intermediate	fast

Figure 1 Intra-arterial digital subtraction angiogram showing a left external iliac thrombosis

units/min. Non-randomised comparisons with low-dose streptokinase have suggested that urokinase is superior.²² Urokinase produced a higher incidence of recanalisation (75 *vs* 45%), a lower rate of significant bleeding (4 *vs* 13%) and a shorter infusion time (18 *vs* 41 h).

Recently tissue plasminogen activator (t-PA) has become popular, although it is much more expensive than streptokinase. Lonsdale and colleagues²³ in a non-randomised study found that t-PA produced a significantly better rate of lysis (58%) than streptokinase (41%). In contrast, Earnshaw failed to show any significant difference in the results for the two agents.²⁴ The only randomised trial that has compared the use of intra-arterial t-PA and streptokinase in the lysis of lower limb thrombosis suggested significant benefits with t-PA.²⁵ The study showed a higher incidence of clinical improvement (100 *vs* 80%), a higher rate of 30-day limb salvage (80 *vs* 60%) and a lower rate of haemorrhagic complications (5 *vs* 30%) for t-PA. Similarly, studies comparing intravenous streptokinase with t-PA in the treatment of acute myocardial infarction have shown a significantly better reperfusion rate for t-PA when lysis is started three hours or later after the onset of symptoms. When treatment is begun within three hours of symptoms, similar results are obtained with both agents.²⁶ Preliminary reports from the ISIS-3 trial comparing intravenous streptokinase and t-PA for acute myocardial infarction have recently been reported.²⁷ The survival rates for the two groups were identical during the first five weeks. However, the incidence of cerebral haemorrhage was significantly greater for t-PA.

Techniques

Under local anaesthetic an intra-arterial digital subtraction angiogram is obtained (figure 1). Ideally, the contralateral femoral artery should be entered for suprainguinal occlusions, and the ipsilateral femoral artery for infra-inguinal occlusions. Occlusive disease in the arm can also be treated but placement of the catheter is often more difficult.²⁸ A guide wire is passed down the artery to the level of the thrombus. A 3–5 french gauge polypropylene catheter is then inserted using the Seldinger technique. The tip of the catheter is placed within the proximal part of the thrombus. The thrombolytic agent is then given. Synchronous occlusions can be treated simultaneously by placing catheters in each occlusion.²⁹ Haematological monitoring is used in some centres but it has not been shown to predict haemorrhagic complications.³⁰

Initial studies involved infusion of low doses of streptokinase (5–10 000 units/h) over many hours. Repeat angiograms are taken at 6–12 hour intervals and the catheter tip is advanced into the remaining thrombus. More recently, a number of techniques have been developed to accelerate the rate of thrombolysis. The aim being to increase the area of interface between thrombus and thrombolytic agent.

Disruption of the thrombus by the passage of a guidewire across the occlusion followed by lacing the entire length of thrombus with lytic agent has been reported to increase the rate of lysis and decrease the dose of agent required.³¹ Using this trans-thrombus technique with high-dose urokinase on 49 patients it was possible to complete lysis in a mean time of 10 hours. The injection of boluses of lytic agent into the thrombus similarly increases the speed of lysis. In a study of 20 patients treated with pulses of t-PA the mean time to achieve lysis was 109 minutes.³² A technique which combines these two approaches has been developed, namely pulsed-spray thrombolysis. It involves the high pressure spray of boluses of lytic agent simultaneously throughout the thrombus. Bookstein³³ reported the results of 41 patients treated with pulsed-spray urokinase. The mean time for completion of lysis was 63 minutes. Other techniques which have been reported to clear thrombus include percutaneous aspiration thrombo-embolectomy and percutaneous mechanical thrombolysis.^{34,35} Both methods involve mechanical disruption of the thrombus and aspiration.

The intra-operative infusion of thrombolytic agents into distal vessels following failed embolectomy or thrombectomy was one of the earliest clinical applications of streptokinase.⁵ More recently, intra-operative thrombolysis has been used to complement balloon catheter thrombo-embolectomy. Beard *et al*³⁶ infused 100 000 units of streptokinase over 30 minutes intra-operatively, in 31 limbs when post-embolectomy angiography had revealed residual thrombus. Complete lysis was achieved in 11 legs and partial lysis in 12 legs.

Following the setting-up of the thrombolysis infusion, the patients are usually closely monitored on an intensive care unit, high-dependency unit, or vascular ward.

Results

Successful recanalisation is possible in 50–90% of cases (see table 2). Early success depends on a number of factors, including age of thrombus,¹⁸ length,¹¹ and site⁸ of occlusion and run off.³⁷ The best results are achieved for short thromboses of proximal arteries, less than one week old with good run off. For example, Barr *et al*³⁸ found a 90% success rate for thromboses of less than one week, compared with 50% for those older than one week. With respect to the site of occlusion, McNamara and Bomberger⁸ analysed 85 patients with lower limb arterial thrombosis. Successful lysis was possible in 90% of supra-inguinal occlusions compared with 69% of those below the inguinal ligament. In general, better results have been achieved for thromboses of native arteries compared with those of grafts. McNamara and Bomberger found that at six months 71% of native arteries were patent compared with 41% of synthetic grafts.

Following successful clearance of thrombus the treatment options include simple anticoagulation, angioplasty, or surgical reconstruction (table 4).

Few studies have compared the results for these three treatments. McNamara found that residual flow-limiting lesions were associated with early re-thrombosis. At six months 8% of arteries and grafts with residual stenotic lesions remained patent, compared with 85% without stenotic lesions. In keeping with these findings, Faggioli *et al*²⁰ found the long-term results for anticoagulation alone were poor. At 24 months, 58% of patient receiving lysis plus angioplasty, 56% of patients receiving lysis followed by reconstruction, and only 26% of patients treated with lysis plus anticoagulation had patent vessels. Most other studies fail to separate the long-term results for these three groups of patients.

Table 4 Options following successful thrombolysis

	Anti-coagulation	Angioplasty	Surgery
Incidence (%)	20	40	40
Indication	no suitable lesion for PTA or surgery	causative stenotic lesion	long segment stenotic disease
Results	poor long term	early re-thrombosis high	peri-operative morbidity may be high

PTA = percutaneous transluminal angioplasty.

Figure 2 Intra-arterial digital subtraction angiogram in the same patient illustrated in figure 1, following successful thrombolysis, reveals a stenosis near the origin of the left external iliac artery (left). This lesion was treated by immediate angioplasty with good improvement in luminal diameter (right)

Incidence of complications following thrombolysis	
• death	1–2%
• non-fatal CVA	1%
• major haemorrhage	5%
• distal embolisation	10%
• minor haemorrhage	15%

Angioplasty is used in 30–40% of patients following successful intra-arterial thrombolysis (figure 2). Again, few studies have separately analysed the outcome for these patients. A recent analysis of 30 patients treated with lysis-assisted angioplasty³⁹ showed a high rate of early occlusion (45%). However, for the 55% of patients whose vessels remained patent beyond one month the long-term patency was as good as with angioplasty alone. High early re-occlusion rates following lysis-assisted angioplasty have been reported by others. Faggioli *et al*²⁰ found that early thrombosis occurred in 22% of patients treated with lysis-assisted angioplasty compared with only 5% who received lysis alone or lysis combined with surgical reconstruction. Hess *et al*³⁷ report the results of 472 patients treated with intra-arterial thrombolysis for lower limb thrombosis, of which 49% also received angioplasty. Early re-occlusion occurred in 25%, being higher for patients also treated with angioplasty than those receiving lysis alone. The best results are achieved for proximal occlusions. In our recent study none of the five patients with an iliac occlusion developed early re-thrombosis.³⁹

The factors predisposing to re-thrombosis include a thrombogenic stimulus provided by exposed intima, platelet and clotting factor activation by lytic agent, and altered flow secondary to residual stenosis.²⁶ Several regimens have been tried as prophylaxis against re-thrombosis, including extended thrombolytic therapy, anticoagulation and antiplatelet agents. Most centres use heparin initially followed by aspirin. Despite this, re-thrombosis has been reported in 10–40% of patients. It has been argued that heparin interferes with the action of the thrombolytic agent and increases platelet aggregation.⁴⁰ Heparin has also been reported to increase the haemorrhagic complications by some investigators.⁴¹ At present the ideal prophylaxis against re-thrombosis remains unproven.

In order to achieve the best results in patients with acute arterial thrombosis selective combinations of lysis, angioplasty, and reconstructive surgery are required. Therefore, it is vital that vascular radiologist and surgeon work closely.

Complications

Intra-arterial thrombolysis is associated with significant complications (see table 2 and box), the most important being local or cerebral haemorrhage. Severe local haemorrhage and cerebrovascular accidents account for death in around 2 and 1%, respectively.⁴ Berridge *et al* reviewed the reported complications in 19 prospective series published between 1974 and 1988.⁴² One per cent of patients suffered a stroke. Major haemorrhage, defined as that requiring transfusion, occurred in 5% of patients, whereas minor haemorrhage occurred in 15%. Distal embolisation occurs in around 12% of limbs undergoing intra-arterial thrombolysis. Usually this is of little consequence, responding to continued thrombolytic infusion. However, in approximately 2% of patients it is associated with sudden clinical deterioration, requiring operative intervention. This phenomenon is more common with lysis of a thrombosed popliteal aneurysm.⁴³ Other rare complications include allergic reactions with streptokinase administration, renal failure secondary to myoglobinuria, and thrombotic complications such as myocardial infarction.⁴

Conclusions

Intra-arterial thrombolysis is becoming first line treatment for acute lower limb thrombosis. In addition to revascularising the limb it often allows definition of the underlying cause of the thrombosis. This may be amenable to angioplasty or reconstruction. While rates of recanalisation are good, the complication rates remain considerable. The best results are achieved for recent proximal occlusions. Further research on defining patients best suited to lysis and the best means of delivering the lytic agent are required.

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