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Acute limb ischaemia: the place of intravenous streptokinase

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Intravenous streptokinase infusions (100 000 units/h) have been used to treat 48 patients, with 50 episodes of acute limb ischaemia who were unlikely to benefit from a surgical approach. These included 17 acute thromboses, 14 late or distal emboli and 19 bypass graft occlusions. Overall, 17 (34 per cent) instances had complete lysis with reappearance of distal pulses and a further 28 per cent had clinical improvement without change in pulse status. Final outcome after 30 days was limb salvage in 60 per cent, amputation in 24 per cent and death in 16 per cent, but this was achieved after eight patients without lysis had vascular reconstructive surgery. Serious complications were infrequent, but included a fatal stroke, a haematemesis and two episodes of distal embolization. The outcome was not related to the duration of ischaemia or the site of occlusion. Lysis was more frequent with emboli (50 per cent) and graft occlusions (47 per cent) than arterial thromboses (6 per cent). Limb salvage was more likely in patients with no neurological deficit in the limb (70 per cent) than if a deficit was present (37 per cent). In conclusion, intravenous streptokinase produced a moderate benefit with low morbidity and has a role in acute limb ischaemia if surgery is inappropriate and intra-arterial lysis unavailable. In particular, selected patients with emboli or graft occlusions without a neurological deficit may be most suitable.

Keywords: Thromboembolism, fibrinolysis, streptokinase

Since Tillett and Garner[1] observed the fibrinolytic activity of proteases produced by streptococci in 1933, the search has continued for safe, effective, methods of achieving *in situ* thrombus dissolution with pharmacological agents. In the 1960s intravenous streptokinase was given to patients with acute limb ischaemia with only limited success and a worrying number of haemorrhagic complications[2–4]. Since Dotter *et al.* described regional fibrinolysis using one-twentieth the concentration of streptokinase given through an indwelling arterial catheter[5], the technique has been shown to be effective with relatively fewer bleeding complications[6,7]. Low-dose intra-arterial streptokinase is an accepted alternative to surgery in the management of selected cases of acute limb ischaemia[8,9]. However, the Dotter technique is time consuming, and requires fairly advanced radiological skills and equipment, and close cooperation between surgeons and radiologists, which may be difficult to organize, particularly out of hours[9]. This method of thrombolytic treatment for acute limb ischaemia has certainly not been uniformly accepted by surgeons.

Intravenous infusions of streptokinase have been widely recommended in the treatment of acute myocardial infarction combining the advantages of efficacy with ease of administration. Despite a paucity of recent data, a survey in 1989 documented that one-third of UK vascular surgeons experienced with thrombolysis had used intravenous streptokinase for acute peripheral arterial ischaemia in the previous 12 months[10]. Intravenous streptokinase infusions are used in Plymouth to treat selected patients with acute limb ischaemia. Experience with the technique in 48 patients has been reviewed retrospectively to try to identify its role in the management of this difficult condition.

Patients and methods

The study included 48 patients with 50 episodes of acute limb ischaemia; there were one upper limb and 49 lower limb occlusions. There were 19 women and 29 men, of median age 68 years (range 31–90 years). Seven patients (15 per cent) had diabetes mellitus and 18 (38 per cent) admitted to regular cigarette smoking. All patients had ischaemic pain at rest. The median duration of ischaemic symptoms was 6 days (range 1–56 days). A total of 13 episodes (26 per cent) had symptoms for less than 24 h, and 28 (56 per cent) for less than 1 week. Sixteen (32 per cent) episodes had signs of a limb neurological deficit on admission and 49 per cent of those assessed had no audible Doppler ankle artery blood flow.

These patients represented a small proportion of those presenting to a vascular unit in a busy district general hospital over a 5 year period. Thrombolytic treatment was selected for the patients if the likelihood of a good result from urgent thromboembolectomy or reconstructive vascular surgery was in doubt. In particular 17 episodes of acute-on-chronic arterial thromboses were selected for thrombolysis because of either advanced age and infirmity of the patient or poor state of the distal vessels. Fourteen episodes of either distal or delayed presentation emboli (range 3–28 days) were thought suitable for thombolysis, along with 19 episodes of acute thrombosis of a bypass graft (*Table 1*).

The patients were given a detailed examination on admission,

Table 1 *Clinical details*

	No. of cases	Percentage
Site of 50 occlusions		
Iliac	13	26
Femoral	29	58
Popliteal	3	6
Brachial	1	2
Bilateral	4	8
both iliacs	2	
both tibials	1	
one popliteal, one femoral	1	
Cause of 50 occlusions		
Native vessel thrombosis	17	34
Embolism	14	28
Graft thrombosis	19	38
femoropopliteal	12	
aortofemoral	6	
iliofemoral	1	

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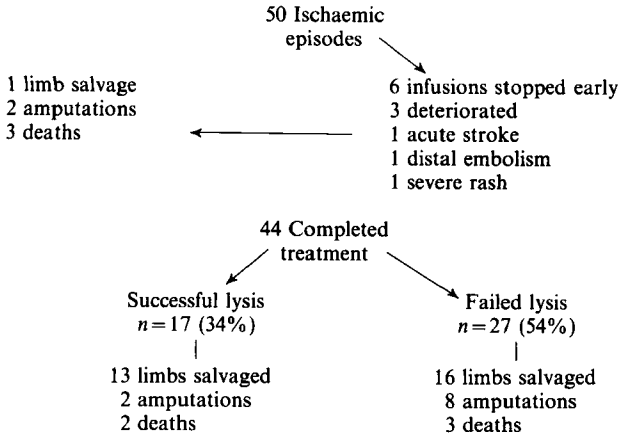

Figure 1 *Results of intravenous streptokinase for acute limb ischaemia with 30 day outcome*

Table 2 *Further procedures after failed thrombolysis*

	Total	Limb salvage
Femoropopliteal bypass	3	3
Aorto/iliofemoral bypass	4	2
Thromboembolectomy	1	0
Sympathectomy	1	1

including documentation of pulses and ankle pressures. On 40 occasions a decision was made at this time that surgery was inappropriate and primary treatment with streptokinase was commenced. Angiography was not performed, to minimize the risk of local haemorrhage. The other ten patients had arteriographs which demonstrated occlusions unsuitable for surgery and these subsequently received thrombolysis between 1 and 10 days later.

Thrombolysis was commenced after an intravenous injection of 100 mg hydrocortisone to prevent allergic reactions. A loading dose of streptokinase was then infused intravenously over 1 h to overcome any circulating streptococcal antibodies. The most frequent loading dose given was 250 000 units, but during the study period it varied from 100 000 to 650 000 units. Subsequently an infusion of 100 000 units/h streptokinase was given for 3 days.

The patients were monitored on a ward where the nurses were used to caring for vascular patients. Hourly observations were recorded throughout the treatment and the patients were closely watched for signs of haemorrhage, particularly at any puncture sites. Coagulation tests and blood counts were measured daily. The ischaemic limb and the pulse state were also carefully observed. The infusion was stopped if there were any complications or if distal pulses reappeared. If there was no change in the ischaemic limb after 72 h, it was not usual to continue streptokinase treatment.

After the streptokinase was stopped, heparin was given to patients with successful lysis, defined as restoration of distal pulses. The heparin was subsequently changed to warfarin and continued for life. If the limb remained painful after streptokinase treatment, it was reassessed and, unless irreversibly ischaemic, angiography was performed followed by vascular reconstruction, if appropriate. After 30 days, or at hospital discharge if sooner, the patients were classified into categories of limb salvage, amputation or death. The patients were subsequently followed up regularly in the outpatient department.

Results

Intravenous streptokinase produced lysis of occluding thrombus with restoration of distal pulses in 17 (34 per cent) instances. Fourteen (28 per cent) limbs improved clinically without objective evidence of change in pulses, 14 (28 per cent) were unaltered and five (10 per cent) deteriorated on treatment. After 30 days (or hospital discharge if sooner) salvage was achieved for 30 (60 per cent) patients, 12 (24 per cent) required amputation and eight (16 per cent) patients died.

Withdrawals

Six patients failed to complete a course of intravenous streptokinase (*Figure 1*). In three cases the ischaemic limb deteriorated during therapy; two patients died from the effects of continued ischaemia, and one limb was saved by successful vascular reconstruction. One further patient suffered a dense stroke and died 5 days later. Another patient with an iliac thrombosis developed distal embolization during treatment and subsequently required bilateral amputation. One patient having a second course of streptokinase, 2 years after the first, developed a severe skin rash.

Successful lysis

A total of 17 (34 per cent) patients had successful lysis with reappearance of distal pulses. After 30 days, 13 remained well. Two patients required amputation following early rethrombosis, 48 h and 96 h respectively after the streptokinase infusion ended. Two patients died, one from a ruptured aortic aneurysm 17 days later while on warfarin, and one 3 days after treatment from unrelieved distal ischaemia despite successful restoration of flow in an occluded aortobifemoral graft. No additional procedures were performed in this group.

Follow-up of this group revealed that all but one of the patients is alive a median of 13 months later (range 4 months to 5 years). Three patients had a late rethrombosis. Two of these necessitated vascular reconstructions, of which one was unsuccessful and ended in amputation.

Failed lysis

Distal pulses were not restored in the remaining 27 patients who completed a 72 h course of streptokinase without event. In this group limb salvage was achieved by 16 patients, five after vascular reconstructions and one after sympathectomy. Eight patients required amputation, three after failed vascular reconstructions. Three patients died, two from the effects of unrelieved ischaemia with bronchopneumonia, and one from an acute myocardial infarction. In the series overall, eight patients had vascular reconstruction after failed thrombolysis, limb salvage being achieved in five cases (*Table 2*).

Follow-up of the 16 patients with limb salvage after failed thrombolysis revealed that all are still alive a median of 15 months later (range 7 months to 5 years). In the follow-up period four patients had further reconstructive surgery and four patients had late amputation. Three patients had troublesome claudication and one a leg ulcer which healed only slowly.

Serious complications with intravenous streptokinase were infrequent (*Table 3*) but included a fatal stroke, two episodes of significant distal embolization (one which resulted in bilateral amputations) and a haematemesis which responded to conservative therapy.

Successful lysis was much more likely for emboli (50 per cent) and graft occlusions (47 per cent) than thromboses (6 per cent). However, limb salvage rates for emboli (57 per cent), graft occlusions (73 per cent) and thromboses (47 per cent) were not significantly different. Lysis rates were better for occluded grafts positioned above the inguinal ligament (57 per cent) compared with those below (42 per cent),

Table 3 *Complications of intravenous streptokinase*

Complication	No. of cases
Major	
Distal embolization	2 (1 amputation)
Acute stroke (died)	1
Haematemesis	1
Minor	
Haematoma	6 (12%)
Heart failure	3 (6%)
Pyrexia	3 (6%)
After second course of streptokinase (2 patients)	
Severe rash	1
Severe phlebitis	1

but the numbers were small and the limb salvage rates similar in each group. The site of the native vessel occlusion bore no relation to outcome, nor did the duration of the arterial ischaemia. Lysis rates were similar whether a limb neurological deficit was present (35 per cent) or absent (31 per cent). However, limb salvage was significantly reduced in patients with a neurological deficit (37 per cent) compared to those without (70 per cent).

Discussion

Initial enthusiasm with intravenous streptokinase in acute limb ischaemia was tempered by a relatively low lysis rate of around 30 per cent and a major complication rate of 10–15 per cent[2–4]. This study reviews the use of streptokinase in three specific groups of patients known to have a poor outcome from conventional surgical techniques, namely those with acute-on-chronic thromboses, those with distal and late presenting emboli and those with graft thrombosis[11,12]. The overall lysis rate of 34 per cent accords with previous publications. Although clinically acceptable lysis rates were achieved for emboli (50 per cent) and graft occlusions (47 per cent), the dissolution rate of 6 per cent for thromboses was disappointing. Limb salvage rates were similar in all groups, but were obtained only after extensive salvage reconstructive surgery in patients with thromboses.

Lysis rates have previously been reported to be best for emboli[2,4], although there have been warnings about the possibility of further embolization caused by the treatment[3]. This has not been confirmed by clinical experience, although distal embolization of a lysing thrombus can occasionally be a serious problem. Several authors have also identified graft occlusions as favourable for intravenous streptokinase[13,14], although the numbers were small and other reports were not confirmatory[15]. Adjunctive surgery has been stated to be required frequently after thrombolysis of graft occlusions[15], but in the present series long-term anticoagulation alone was sufficient for prolonged patency in most patients. The severity of the ischaemia at presentation was confirmed as a significant predictor of outcome in this study[2], but the duration of ischaemia did not appear to be as crucial as others have suggested[3].

The major complication rate from thrombolysis was low, although one patient died from a stroke and one required amputations after distal embolization. This rate is lower than previously reported, possibly because of exclusion of patients at high risk of haemorrhage[16] and avoidance of diagnostic angiography in most patients, which reduced the risk of bleeding from arterial puncture sites. A non-invasive assessment seems ideal for these patients. A small risk of serious haemorrhage is unavoidable in thrombolytic treatment and it is unlikely that the present rate can be reduced[17].

One possibility of improving the results of intravenous thrombolysis is to use new fibrin-specific agents. These agents have an affinity for fibrin which may increase dissolution of the occluding thrombus. Their specificity may also reduce the degradation of plasma fibrinogen which occurs with streptokinase therapy and is the main cause of haemorrhagic complications. Anistreplase (Eminase®, Beecham Pharmaceuticals, Brentford, UK) is an acylated complex of plasminogen and streptokinase which results in prolonged fibrinolytic activity. Anistreplase can be given as a single intravenous bolus for acute myocardial infarction. However, when a smaller dose (5 mg, equivalent to 180000 units streptokinase) was given 8 hourly over 3 days to patients with acute peripheral arterial occlusions, the clinical results were no better than those reported with intravenous streptokinse, and haemorrhagic complications were frequent[18,19]. Tissue plasminogen activator (t-PA) (Actilyse®, Boehringer Ingelheim, Bracknell, UK) is a naturally occurring fibrinolytic agent produced by recombinant DNA technology in sufficient quantities for clinical use. Exceptional results have been reported with intra-arterial t-PA for acute limb ischaemia[20] and, in a randomized trial, lysis rates with intra-arterial t-PA (100 per cent) were far superior to those recorded with intravenous t-PA (45 per cent)[21]. Lastly, the intermittent use of high doses of intravenous streptokinase, or 'burst therapy', has been shown to allow plasma fibrinogen time to recover between injections, but has not yet been shown to have any advantage over continuous infusions[22].

Randomized comparison of intravenous streptokinase and low-dose intra-arterial streptokinase have yet to be performed in similar patients. However, in a randomized study, lysis with intra-arterial streptokinase (80 per cent) was superior to that with intravenous t-PA (45 per cent)[21]. Combined with information from the large number of open studies that intra-arterial streptokinase produces lysis in about two-thirds of patients treated[6,7], it is reasonable to state that the latter is presently the thrombolytic method of choice in acute limb ischaemia.

It is the opinion of several recent reviewers that thrombolytic therapy is a real alternative to surgery in selected cases of acute limb ischaemia[8,9], and that low-dose intra-arterial streptokinase is currently the gold standard against which other agents should be tested[23]. Early results have suggested that t-PA may replace streptokinase as the agent of choice[24].

However, there is still a role for intravenous streptokinase in selected cases, particularly if the intra-arterial route is impossible for technical reasons, or not available. In particular, patients with distal and late presenting emboli and those with graft occlusions may be most suitable, especially if there is no limb neurological deficit. In the long run the ideal method of treatment of these specific groups of patients will require a randomized comparison.

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Short note

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Dynamic angioplasty of total arterial occlusions

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Percutaneous transluminal balloon angioplasty is an effective technique for the treatment of arterial stenosis and short occlusions. However, when used for long and chronic total occlusions it has a relatively high failure and complication rate[1]. Alternative techniques including a variety of laser and mechanical devices are developing rapidly[1]. This is a report of the use of a percutaneous dynamic angioplasty device – the Kensey catheter (Theratec and Cordis, Miami, Florida, USA).

Patients and methods

Twenty men, aged 54–74 years, with history of disabling intermittent claudication were included. Median claudication distance was 30 yards, range 0–70 yards; two patients had pain at rest. Mean duration of symptons was 2·5 years. Angiography demonstrated total occlusion in 3 iliac and 17 femoral arteries (3–16 cm, mean = 10 cm). In all patients, an attempt to cross the occlusions with a steerable guide wire failed. Percutaneous dynamic angioplasty was carried out under local anaesthesia using an 8 Fr (2·7 mm) Kensey catheter (*Figure 1*) at a cam speed of 40 000–80 000 revolutions per minute. The technique was approved by the ethical committee and informed consent was obtained from all patients. When successful, the procedure was followed by balloon dilatation of the recanalized segment.

In addition to clinical follow-up, ankle/brachial Doppler pressure index (ABPI) and hyperaemia-induced limb blood flow (LBF) using ^{99}Tc-labelled albumin[2] were measured before recanalization and at 3 weeks, 3 months and 6 months after each procedure. Long-term patency was assessed by re-angiography 9–12 months after recanalization. All patients received 75 mg aspirin (daily) and 100 mg dipyridamol (three times a day) starting one day before the procedure and continuing until re-angiography. All results are expressed as mean(s.e.m.). The paired Student *t* test was used to assess the significance of changes in ABPI and LBF.

Results

In all patients it was possible to reach the lesion with a steerable guide wire. However, this failed to cross the occlusion. Dynamic angioplasty using the Kensey catheter successfully recanalized the whole length of the occlusion in 15 patients (*Figure 2*). In three patients, only part of the occluded segment was recanalized; in this group complete recanalization was prevented by dissection in two cases and by perforation in one. In the remaining two patients early perforation precluded any recanalization. There was no correlation between the length of the occlusion and the result of dynamic angioplasty.

In the 15 lesions that were successfully recanalized, a small dissection was observed angiographically in three (*Figure 2b*) and contrast extravasation was observed in two. In one patient early reocclusion (within a few hours) necessitated repeat balloon angioplasty which was associated with thrombotic embolism. However, no atheromatous embolism was observed during the use of the Kensey catheter.

Full recanalization resulted in symptomatic improvement in all 15 patients. There was a significant improvement in ABPI and LBF (*Table 1*). Some symptomatic improvement was also felt by two of the three patients in whom recanalization was incomplete. No worsening of claudication was experienced in those two patients with primary failure. There was no fall in ABPI or LBF in patients who had no or incomplete recanalization (*Table 1*).

Re-angiography was performed in 10 of 15 patients who had full recanalization. Patency was demonstrated in eight.

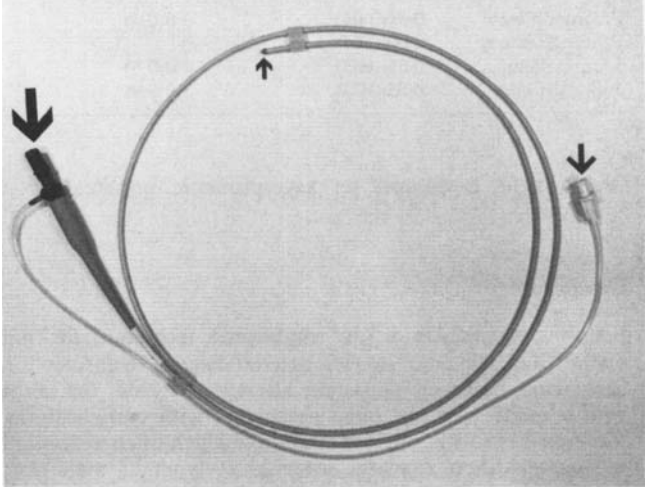

Figure 1 *The Kensey catheter: rotating cam at the tip (middle arrow); connection to motor (left arrow); flushing port (right arrow)*