Selective infusion of streptokinase for arterial thrombosis

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We have treated 13 patients with limb-threatening ischemia caused by acute arterial thrombosis with selective arterial infusion of streptokinase. The indications for thrombolytic therapy included medical contraindication to surgery, surgically inaccessible thrombi, arterial thrombosis following percutaneous transluminal angioplasty, and thrombosed distal arterial bypass. Patients were evaluated with arteriography, Doppler segmental arterial pressure studies, and coagulation profile. Objective evidence of complete or partial thrombolysis was demonstrated in 11 of the 13 patients (85%). Treatment after thrombolytic therapy included percutaneous transluminal angioplasty in six patients and distal bypass in two patients. Of five patients who had received no additional treatment, three required amputation. Overall limb salvage was achieved in 10 of the 13 patients. The most serious complications were puncture site bleeding in five patients, acute renal failure in one patient, and retroperitoneal hemorrhage in another patient. Bleeding was more frequent in patients with decreased serum fibrinogen levels. Although lysis of acute arterial thrombosis can be achieved, thrombolytic therapy alone will allow limb salvage in only a few patients. Selective thrombolytic therapy with streptokinase must be used with caution and is associated with serious complications.

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Limb loss following acute arterial occlusion can usually be avoided with prompt thrombectomy, embolectomy, or arterial reconstruction. For some patients in whom operative intervention is not possible, enzymatic thrombolysis with streptokinase or urokinase can restore arterial circulation. These commercially available agents activate plasminogen to plasin and have usually been administered in high doses by intravenous infusion. Although this approach has been largely successful in achieving thrombolysis, systemic therapy has been associated with considerable rates of morbidity and mortality.\(^1,5,8,12\) The incidence of serious complications with systemic infusion has been reported to be as high as 30% to 50%,\(^1,7,12\) and treatment-related deaths have occurred in 5% to 15% of patients.\(^1,5,8\)

Complications include hemorrhage, stroke, "rebound" hypercoagulability, allergic reactions, and acute renal insufficiency.\(^1,5,8,10,12\)

In an effort to reduce the morbidity associated with thrombolytic therapy, several investigators have employed selective arterial infusion of streptokinase directly into the thrombus.\(^2,3,6\) This approach offers the potential advantage of localizing thrombolysis to the site of obstruction without the high risk of hemorrhage associated with systemic therapy.\(^2,3\) We have evaluated this therapeutic approach in 13 patients with acute ischemia. All patients had impending loss of limb and were not candidates for immediate arterial reconstruction. Streptokinase was infused locally through an intra-arterial catheter, and in some patients successful thrombolysis was later combined with elective arterial reconstruction or percutaneous transluminal angioplasty.

**PATIENTS AND METHODS**

Thirteen patients were treated with selective arterial infusion of streptokinase at the University of Chicago.
Hospitals and Clinics from July 1981 to July 1982. All the patients had acute limb-threatening ischemia caused by thrombosis or embolism. The duration of symptoms ranged from 3 hours to 1 month. Ischemia involved the lower extremity in 12 patients and the upper extremity in 1 patient. Specific indications for thrombolytic therapy included medical contraindications to surgery (four patients), surgically inaccessible thrombi (two patients), arterial thrombosis following percutaneous transluminal angioplasty (four patients), and thrombosed distal arterial bypasses (three patients). Ten of the patients with lower extremity arterial thromboses had poor distal runoff vessels (one or no distal tibial vessel demonstrable on arteriographic evaluation). Patients at increased risk for thrombolytic therapy were excluded from the treatment protocol. Contraindications included allergy to streptokinase, streptokinase infusion within the previous 3 months, recent major surgery including biopsies at inaccessible sites, defective hemostasis, untreated hypertension, recent cerebrovascular accident, liver or renal disease, potential macroembolism, and concurrent anticoagulant administration.

All the patients underwent complete extremity arteriography, Doppler segmental arterial pressure studies, and coagulation studies including platelet count, prothrombin time, partial thromboplastin time, fibrinogen level, and determination of fibrin degradation products prior to and after thrombolytic therapy. Arteriograms were performed according to the transfemorai Seldinger catheter technique. Following the demonstration of arterial thrombi and efforts to identify any suitable distal vessels, a 4F angiographic catheter was placed as close to the thrombus as possible to deliver a maximal concentration of streptokinase to the site of occlusion. We preferred to introduce the catheter through the contralateral common femoral artery to reduce the risk of hematoma formation during infusion. In most cases streptokinase infusion was begun at the time of the initial contrast study.

Streptokinase was administered at a rate of 5000 U/hr; no loading dose was administered. Although many patients had been receiving intravenous heparin at the time of initial contrast studies, heparin was discontinued during streptokinase infusion. Distal lower extremity perfusion was objectively assessed by recording segmental Doppler ultrasound flow velocity and pressure measurements. The ratio of ankle systolic to brachial systolic pressure (ankle:brachial index, ABI) was calculated as described in a previous report.13

Patients were observed in an intensive care unit. Vital signs and arterial puncture sites were monitored hourly and coagulation studies performed every 12 hours. Patients were treated with systemic antibiotics during streptokinase infusion. Follow-up arteriograms
and Doppler pressure studies were performed every 24 hours or more often as necessary.

RESULTS

Most patients received thrombolytic therapy for 48 hours (range 24 hours to 5 days). It was found that in successful applications, thrombolysis occurred within the first 48 hours; extending the infusion time offered little therapeutic advantage. Objective evidence of thrombolysis (complete or partial) was demonstrated by repeat arteriography for 11 of the 13 patients (85%). Treatment was least successful in patients with popliteal artery occlusions and no demonstrable runoff vessels. Thrombolysis was incomplete or absent in four of six such patients.

Limb salvage was achieved in 10 of the 13 patients. Circulation was not restored in two patients and amputation was required. In two patients thrombolytic therapy alone was successful in achieving limb salvage (Fig. 1). In six patients with successful thrombolysis, subsequent arteriography uncovered occlusive atherosclerotic lesions that were treated with percutaneous transluminal angioplasty (Fig. 2). Another patient, in whom patency of an occluded femoropopliteal bypass was achieved, had no runoff vessels and required below-knee amputation (Fig. 3). Two additional patients demonstrated distal runoff vessels below the knee suitable for arterial reconstruction following thrombolytic therapy and underwent femoral-peroneal bypasses that have remained patent.

Objective hemodynamic response was determined by Doppler arterial pressure measurements. Pretreatment ABIs were $0.18 \pm 0.08$ (mean $\pm$ SEM). Following selective infusions of streptokinase, the mean ABI increased to $0.49 \pm 0.09$ ($P < 0.05$, paired $t$ test). Appropriate treatment of underlying arterial lesions including percutaneous transluminal angioplasty or distal arterial bypass, increased the ABI further to $0.62 \pm 0.12$ ($P < 0.01$).

Changes in coagulation studies during selective streptokinase infusion are shown in Table I. Thrombolysis was associated with an increase in fibrin degradation products and a decrease in fibrinogen levels. Although there were statistically significant increases in prothrombin and partial thromboplastin times compared to the pretreatment values, neither of these changes was great enough to be considered clinically relevant. In fact, routine laboratory studies were of limited usefulness in predicting the outcome of thrombolytic therapy or the risk of bleeding complications. It was noted, however, that in four of six patients with bleeding complications the plasma fibrinogen levels decreased below the normal value of 100 mg/dl. This led to our current recommendation that patients with declining fibrinogen levels receive fresh-frozen plasma.

Minor complications attributed to thrombolytic therapy included fever in three patients and a flu-like syndrome in one. Puncture site bleeding with minor ecchymoses and groin hematomas occurred in five
Fig. 3. Roentgenogram of a 58-year-old man with severe ischemia following thrombosis of a saphenous vein femoropopliteal bypass (A) performed 3 weeks earlier. There was no reconstruction of distal bypassable vessels (B). After 48 hours of streptokinase infusion into the common femoral artery, patency of the saphenous vein bypass (C) and blind popliteal artery segment (D) was restored. More distal reconstruction was not possible because of lack of outflow vessels, and rethrombosis occurred 24 hours after the streptokinase infusion was discontinued. Below-knee amputation was required.

Table I. Coagulation studies during streptokinase infusion (mean ± SEM)

<table>
<thead>
<tr>
<th>Test</th>
<th>Before streptokinase</th>
<th>24 Hours streptokinase</th>
<th>48 Hours streptokinase</th>
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</thead>
<tbody>
<tr>
<td>Hematocrit (%)</td>
<td>36 ± 1.6</td>
<td>36 ± 1.4</td>
<td>32 ± 1.4</td>
</tr>
<tr>
<td>Platelets (×10^9/mm^3)</td>
<td>328 ± 35</td>
<td>273 ± 40</td>
<td>277 ± 28</td>
</tr>
<tr>
<td>Prothrombin time (sec)</td>
<td>12.4 ± 0.39</td>
<td>15.5 ± 0.54*</td>
<td>14.8 ± 0.51*</td>
</tr>
<tr>
<td>Partial thromboplastin time (sec)</td>
<td>40.2 ± 4.6†</td>
<td>28.2 ± 0.5*</td>
<td>30.8 ± 3.8</td>
</tr>
<tr>
<td>Fibrinogen (ng/dl)</td>
<td>388 ± 76</td>
<td>155 ± 48*</td>
<td>167 ± 34*</td>
</tr>
<tr>
<td>Fibrinogen degradation products (µg/µl)</td>
<td>&lt;10</td>
<td>&gt;40*</td>
<td>&gt;40*</td>
</tr>
</tbody>
</table>

*P < 0.05 (analysis of variance)
†Effect of heparin prior to streptokinase infusion.

patients. Thrombosis of the superficial femoral artery proximal to the tip of the infusion catheter occurred in two patients during streptokinase infusion. In these cases the catheters were withdrawn into the common femoral artery and infusions continued. This maneuver proved successful in achieving thrombolysis in both instances. Rebound thrombosis following the termination of infusion was noted in one patient. Another patient had evidence of distal microembolization during treatment. A single patient developed transient nonoliguric acute renal failure, presumably resulting from multiple contrast injections.

The only life-threatening complication in this series was the development of a retroperitoneal hemorrhage and hypotension in one patient three days following the discontinuation of streptokinase infusion. At this time, the patient was again receiving intravenous heparin. Abdominal exploration was performed and no specific bleeding site identified.

DISCUSSION

The mechanism of action of the thrombolytic agents, streptokinase and urokinase, has recently been reviewed by Sharma et al. Streptokinase is a product of group C β-hemolytic streptococci and produces clot lysis by activation of the human fibrinolytic system. Streptokinase combines with the inactive proenzyme plasminogen to form an activator complex. This com-
plex then enzymatically converts available plasminogen to plasmin, the active fibrinolytic enzyme. The kinetics of this reaction can be modified by streptokinase antibodies and circulating plasmin inhibitors. Active plasmin has relatively nonspecific activity and produces enzymatic degradation of fibrin, fibrinogen, prothrombin, and factors V and VIII. Streptokinase activates both circulating plasminogen and the thrombus-bound fraction. Thrombolysis by systemic infusion is dependent upon the activation of circulating plasmin, which then externally and nonselectively digests thrombi wherever they may occur. Loading and high infusion doses are thus required to overcome systemic inhibitory mechanisms. The predictable end result is generalized thrombolysis associated with a profound coagulopathy and high risk of bleeding complications.

Selective infusion delivers a higher concentration of streptokinase to the clot and activates thrombus-bound plasminogen more effectively. Importantly, the drug is less exposed to circulating antibodies and inhibitors. This allows a lower total infusion dose, and theoretically produces fewer systemic effects and less risk of complication.

The experience with systemic infusion suggested that acute thrombi respond better than chronic thrombi and that proximal lesions respond better than distal lesions. These studies are often difficult to interpret because thrombolytic therapy was used as an alternative rather than an adjunct to conventional surgical intervention. Patient populations in these studies were not well characterized other than by acknowledgment of the presence of peripheral arterial occlusive disease. Precise symptoms and hemodynamic alterations were often not well documented before or after therapy. Results were often defined solely according to radiographic criteria.

We have followed the recommendation of several authors that thrombolytic therapy be restricted to acute thrombi of less than 2 month's duration. Our approach has been to restrict thrombolytic therapy to patients with limb-threatening ischemia for whom surgical options were limited. These patients present with excessive risk for anesthesia and surgery. Specific contraindications included active wound infections and distal microembolization inaccessible to standard surgical techniques. Others have applied selective thrombolytic therapy to thromboses following percutaneous transluminal angioplasty. We have shown that thrombolytic therapy also can be used to uncover atherosclerotic lesions subsequently treatable by transluminal angioplasty.

Both Persson et al. and Husson et al. have demonstrated the effectiveness of systemic thrombolytic therapy in restoring patency of occluded bypass grafts. Although this would appear to be an attractive option in the treatment of thrombosed saphenous vein grafts, it is important to recognize that graft stenoses or deterioration in distal runoff vessels must be identified and treated in order to achieve long-term patency. Persson et al. found that thrombolysis as sole therapy was uniformly unsuccessful. This parallels our experience with three bypass grafts; patency was achieved in all three, but in two cases limb loss resulted from inadequate distal runoff vessels.

Thrombolytic therapy has been associated with serious hemorrhagic complications, particularly spontaneous intracerebral hemorrhage. Other manifestations of systemic coagulopathy have been puncture site bleeding and retroperitoneal hemorrhage. Selective low-dose infusion of streptokinase has been reported to reduce the rates of hemorrhagic complications and death. However, Chaise and associates have noted that even local infusions result in depletion of clotting factors, particularly fibrin. The degree of coagulopathy appears to be an individual response. Furthermore, no laboratory tests currently available reliably predict the level of local or systemic fibrinolysis or the risk of hemorrhage. In our experience, four of six patients with bleeding problems manifested substantial decreases in serum fibrinogen. We have thus replaced fibrinogen with fresh-frozen plasma when serum fibrinogen levels fall below 100 mg/dl. While Chaise and colleagues have successfully used thrombolytic therapy by the selective infusion technique in the immediate postoperative period, this practice must be approached with great caution. Based on our experience, even selective infusion can result in major hemorrhagic complications at distant sites and for several days thereafter. This risk is higher for patients receiving other anticoagulants or antiplatelet drugs.

We have attempted to better define clinical situations in which thrombolytic therapy is a useful adjunct to conventional therapy such as arterial bypass and percutaneous transluminal angioplasty. Although lysis of acute arterial thrombi can be achieved, thrombolytic therapy alone will allow limb salvage in only a few patients. Despite the theoretical safety of local infusion, systemic coagulopathy of varying degrees can and does occur. It remains to be seen if specific component replacement will reduce these complications.

REFERENCES


*See references 1, 4, 5, 7, 8, 12.


