Some Clinical Problems in Patients Undergoing Thrombolytic Therapy

W. M. ROBERTS

SUMMARY

A total of 25 patients (7 with arterial occlusion and 18 with venous thrombosis) were treated with streptokinase for 72 hours, followed by heparin for 24 hours. The clinical problems, complications and results obtained are discussed. Within the limits imposed by the study, it is concluded that streptokinase offers safe and effective therapy for early iliofemoral venous thrombosis.

Surgeons are constantly concerned with the prevention, early diagnosis and treatment of venous thrombosis in seriously ill and postoperative patients. Prophylactic treatment with low doses of heparin holds the greatest promise. Heparin treatment should, however, always be combined with other methods which are known to have a beneficial effect, especially in elderly patients. These methods include adoption of a mild Trendelenburg position during and after operation, early movements, especially pedalling against resistance; avoidance of positions creating stasis, elastic compression and proper hydration of the patient. In spite of these measures, venous thrombosis still occurs frequently. Early diagnosis is aided by regular clinical assessment and by the use of screening methods, especially ultrasonography and radioiodinated fibrinogen. Suspected thrombosis should be confirmed by ascending venography.

It is unfortunate that these diagnostic techniques are not infallible and their limitations should be appreciated by the clinician. More accurate methods are still being sought. Considerable controversy still exists about the best form of treatment. The efficacy and safety of the available methods must be firmly established. In this paper I hope to contribute to certain aspects regarding the safety of streptokinase therapy for venous thrombosis.

PATIENTS AND METHODS

The patients described here had critical arterial and venous disorders and they were treated in private practice during the past 6 years. Most of the patients had already received other forms of therapy without improvement, and had been admitted to a variety of private institutions where facilities for investigation were often lacking. Because patients with iliofemoral venous thrombosis run a great risk of developing major pulmonary embolism and chronic venous insufficiency, it was not considered justified to transfer such patients to other institutions in order to do venography. In most of these cases treatment was started as soon as the situation required it.

Apart from clinical assessment, the platelet count, prothrombin index and accelerated partial thromboplastin time of each patient were determined. Serum proteins and other components were analysed when indicated. Drugs known to enhance haemorrhagic tendencies were excluded. Causes of a swollen limb, such as deep trauma, deep-seated haemorrhage, cellulitis, congestive cardiac failure

Cape Town

and lymphoedema were largely excluded by careful clinical assessment. Patients with venous obstruction due to tumours or other masses are not included in this series. Contra-indications to thrombolytic therapy were rigidly observed, namely the immediate postoperative state, recent cerebrovascular accident, hypertension with a diastolic blood pressure exceeding 100 mmHg, a platelet count under 100 000/μl, active gastro-intestinal ulceration or a bleeding tendency. The interval after operation should be individually assessed.

Treatment

Treatment was standardised in all cases. Arterial disease was proved by arteriography and most patients with venous obstruction had venographic investigation before treatment. For obvious reasons, few had venography after therapy. This series is therefore largely uncontrolled.

Therapeutic substances were administered through an arm vein. The affected part was elevated, but no elastic supports, diuretics or antibiotics were used as a routine. Hydrocortisone 100 mg was injected intravenously. The loading dose of 600 000 to 750 000 units of streptokinase was administered within about 20 minutes, followed by 100 000 units hourly for a minimum of 72 hours. At about the 36th hour after starting treatment, the patient was given a loading dose of Coumadin. Six hours after the conclusion of streptokinase therapy, an intravenous infusion of heparin was commenced and continued for approximately 24 hours. It was then stopped 8 hours before determination of the prothrombin index. Anticoagulant therapy with Coumadin was continued for a variable and usually prolonged period.

Early in this series, strict haematological control was used, particularly for the thrombin time. Control was later abandoned because one of the patients who bled did so in spite of normal test results. Furthermore, the delay in obtaining results from the laboratory made the procedure impractical. An acceptably low complication rate was achieved by careful selection of patients and rigid adherence to the intravenous schedule. Variations in the rate of infusion were simply not permissible. There seems to be little guidance from any laboratory investigation upon the likelihood of a serious bleeding problem during treatment.

RESULTS

Acute-on-Chronic Arterial Occlusion

Seven patients were treated for critical ischaemia. 6 men and 1 woman, with a mean age of 67 years (Table I). The woman, aged 42 years, had mild hypertension, severe aortic arch disease, occlusion of the palmar arches and ischaemia of two fingers. The 6 men were all seriously ill from cardiac, respiratory and other disease. All had advanced diffuse atherosclerosis, long-standing claudication, and recent femoropopliteal or distal occlusion which caused critical ischaemia or gangrene. Three men had chronic atrial fibrillation. Arterial surgery was attempted in 2 men with gangrene.

In 4 patients in whom no operation had been performed, long-lasting clinical improvement was achieved with return of pulses in 2 and disappearance of ischaemic manifestations in the other 2. There was no improvement in 1 patient in whom an occluded Dacron graft, inserted 1 year previously, was not re-opened by treatment, but the graft had occluded about 10 days previously. In the 2 patients in whom arterial reconstruction for peripheral gangrene was attempted, therapy was interrupted by haemorrhage from arteriotomy wounds 5 and 10 days respectively after operation. One patient later required an amputation below the knee and the other died of cerebral embolism 12 hours later. Another man, with initial restoration of pulses, died of cerebral embolism 3 months after treatment. Both patients who died of cerebral embolism suffered from chronic atrial fibrillation.

Venous Thrombosis

There were 18 patients who were treated for extensive venous thrombosis. This group consisted of 13 men and 5 women with a mean age of 48 years (Table II). One patient had subclavian vein thrombosis and initially responded well to thrombolytic therapy. He stopped taking Coumadin one month later, relapsed, and later had a poor result after thrombectomy.

The other 17 patients all had florid iliopopliteal venous thrombosis. Many had severe cardiovascular disease, and 2 had previously undergone arterial surgery. Six had a history suggestive of previous venous thrombosis and 2 had

<table>
<thead>
<tr>
<th>Case</th>
<th>Sex</th>
<th>Age</th>
<th>Atrial fib.</th>
<th>Arterial surgery</th>
<th>Result</th>
<th>Follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>M</td>
<td>72</td>
<td>+</td>
<td>+</td>
<td>Pulses +</td>
<td>Died 4 yrs later. Myocardial infarction</td>
</tr>
<tr>
<td>2</td>
<td>M</td>
<td>72</td>
<td>+</td>
<td>Dacron graft</td>
<td>Pulses +</td>
<td>Died 3 mo. later. Cerebral embolism</td>
</tr>
<tr>
<td>3</td>
<td>F</td>
<td>42</td>
<td>-</td>
<td>Endarterectomy</td>
<td>No ischaemia</td>
<td>Alive, well</td>
</tr>
<tr>
<td>4</td>
<td>M</td>
<td>80</td>
<td>-</td>
<td>-</td>
<td>No ischaemia</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>M</td>
<td>69</td>
<td>-</td>
<td>Dacron graft</td>
<td>Poor</td>
<td>Claudication 5 yrs later</td>
</tr>
<tr>
<td>6</td>
<td>M</td>
<td>72</td>
<td>-</td>
<td>Endarterectomy</td>
<td>Haemorrhage</td>
<td>Late BKA</td>
</tr>
<tr>
<td>7</td>
<td>M</td>
<td>69</td>
<td>+</td>
<td>Endarterectomy</td>
<td>Haemorrhage</td>
<td>Died 12 h later. Cerebral embolism</td>
</tr>
</tbody>
</table>

BKA — below-the-knee amputation.
An excellent response was attained in 7 limbs (36.8%), including the patient with phlegmasia caerulea dolens. A good result followed treatment in 6 limbs (31.6%), giving a most gratifying clinical improvement in 68.4%. A fair result was obtained in 4 limbs (21.1%). All these patients had a history of previous venous thrombosis. Two patients had a poor result (10.5%). One was the patient with recurrent subclavian vein thrombosis. The other was the man who had his therapy interrupted owing to bleeding from an arteriotomy wound. This patient is the only one in this series of iliofemoral thrombosis who required subfascial ligation of perforators for chronic venous insufficiency. He still has excellent pulses 5 years later.

It was clear from observation of these patients that the best results followed early treatment. It is also noteworthy that oedema often persists for several days after cessation of treatment, possibly owing to continuing thrombolysis.

**Complications**

Haemorrhage from arteriotomy wounds during streptokinase therapy occurred in 3 patients, on the 4th, 5th and 10th postoperative days, respectively. The bleeding in all these patients was readily controlled by neutralising streptokinase. Secondary haemorrhage due to infection could not be excluded in the 2 patients with peripheral gangrene, although no organisms could be grown in cultures from the wounds.
Reactions to Therapy

Reactions to the loading dose consisted mainly of body aches, slight elevation of, and a subsequent drop in blood pressure, and tachycardia. In only 1 patient was it necessary to reduce the loading dose. This man had serious myocardial disease and atrial fibrillation. In the other patients it was found that reactions to the loading dose could easily be controlled by slight variation in the rate of infusion, and yet the dose could be given within about 20 minutes. Later reactions during therapy consisted mainly of body aches, anorexia, nausea, confusion and pyrexia. These reactions seldom required treatment and subsided as soon as therapy was completed. Severe allergic manifestations were not observed.

DISCUSSION

The results obtained in this small series of patients with arterial occlusion make it apparent that thrombolytic therapy has a place in the management of critical ischaemia in patients in whom disease precludes arterial surgery. This applies particularly to the femoropopliteal and distal arterial segments.

The three instances of haemorrhage from arteriotomy wounds suggest that thrombolytic therapy may be contraindicated within 2 weeks or more after arterial operations, particularly in elderly, debilitated patients with peripheral gangrene, in view of the possibility of infection. Two patients who bled were probably treated too soon after operation, although at that time 72 hours was considered an adequate interval. The possible use of streptokinase postoperatively should be individually assessed according to the age and general condition of the patient, the type of operation which had been performed, and the possibility of secondary haemorrhage due to infection. In most instances, it is probably safe to administer streptokinase within 5-7 days of operation. Determination of the safety interval after surgery will only be possible when the results of postoperative treatment after a variety of surgical procedures can be analysed.

Two of the 3 patients with chronic atrial fibrillation died of cerebral embolism. Neither died during thrombolytic therapy, but the effect of streptokinase treatment on such patients needs clarification.

The clinical diagnosis of early venous thrombosis is probably not more than 60% accurate, and diagnosis should always be confirmed by venography. Since venography was not performed in all cases in this series, the results must be interpreted with caution. In most instances, venous thrombosis commences in the soleal venous plexuses and small veins of the leg before involving the iliofemoral segment, which is seldom involved as a separate entity. This fact probably enhances the validity of clinical diagnosis in this series.

It is very difficult to assess the time of onset and rate of progression of venous thrombosis without the use of regular screening methods. It is well known that clinical improvement may occur in the absence of radiological improvement. Venography performed in patients who have been referred for relatively minor varicose veins, and who give no history suggestive of previous venous thrombosis, has occasionally demonstrated partial or complete occlusion of femoral or iliac veins. The venographic interpretation of the results of treatment for an apparently recent thrombosis should therefore include unequivocal evidence of prethrombotic normality, since incomplete clearance in such cases is caused by the presence of an unsuspected organised thrombus.

A comparison of available methods of treatment in essence boils down to surgical thrombectomy as opposed to treatment with streptokinase or intravenous heparin. Thrombectomy should be performed soon after the onset of venous thrombosis; often this is a time when the patient is critically ill. In iliofemoral venous thrombosis a direct approach to the proximal point of obstruction involves a major surgical procedure. The least traumatic operation is performed via the femoral veins, using Fogarty balloon

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**TABLE IV. THROMBOLYSIS COMPARED WITH ANTI-COAGULATION: VENOUS THROMBOSIS FOLLOWED BY RADIO-ISOTOPES OR BY PHLEBOGRAPHY**

<table>
<thead>
<tr>
<th>Streptokinase</th>
<th>Heparin</th>
</tr>
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<tbody>
<tr>
<td>Study Number</td>
<td>Good</td>
</tr>
<tr>
<td>1, 2</td>
<td>29</td>
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<tr>
<td>3</td>
<td>9</td>
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<td>5</td>
<td>5</td>
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<tr>
<td>6</td>
<td>10</td>
</tr>
<tr>
<td>Total</td>
<td>73</td>
</tr>
</tbody>
</table>

Note: In study 3, 9 of 10 other patients treated with ancrad showed a poor result.


* Patients with rethrombosis after iliofemoral thrombectomy.
catheters, and has the advantage of being possible under local anaesthesia. The high incidence of complications, such as haemorrhage, infection, pulmonary embolism, and rethrombosis, coupled with its failure to preserve valvular function, imply that it should only be considered for patients with phlegmasia caerulea dolens with impending gangrene, and perhaps in early isolated iliac vein thrombosis. Thrombolysis is the only available method for clearing thrombus from the internal iliac veins, the soleal venous sinuses and the small veins of the calf. Comparisons of streptokinase and heparin therapy have been reported in many series (Table IV). The evidence in these series is in favour of streptokinase, particularly in respect of complete clearance of thrombus and preservation of valvular function, and especially if treatment can be commenced within 36 hours of the onset of thrombosis. It still remains to be established whether preservation of valvular function will reduce the later incidence of chronic venous insufficiency, but the outlook appears hopeful as judged by patients in this series, more than half of whom have been followed for 3-6 years. This small series of cases of florid iliofemoral venous thrombosis is comprised of patients who were often treated under difficult circumstances. While I accept the fallibility of clinical assessment alone, the long-term results have been gratifying. No patient who was treated with streptokinase has later required surgery for chronic venous insufficiency. Pulmonary embolism was not detected in this series, and there were no serious complications. I therefore feel that with careful selection of patients and rigid adherence to the intravenous schedule, iliofemoral venous thrombosis can be effectively and safely treated by using a standard regimen of streptokinase therapy. I consider it to be the treatment of choice for early venous thrombosis.

I wish to thank Dr James Ware for his assistance in the preparation of this paper.

REFERENCES