PAPERS AND ORIGINALS

Treatment of Deep Vein Thrombosis with Streptokinase

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Summary

From September 1962 to May 1972 145 patients with acute or subacute deep vein thrombosis confirmed by phlebography were treated with streptokinase. During the same period 42 patients considered unfit for thrombolytic therapy were treated with herapin and oral anticoagulants. The results, assessed by repeat phlebography, in 93 of the patients treated with streptokinase were compared with those in the 42 patients treated with heparin. The age, sex, and severity of occlusion were roughly similar in both groups. Streptokinase treatment was successful in 42%, partially successful in 25%, and unsuccessful in 32% of the 93 patients compared with none, 10%, and 88% respectively in the 42 patients treated with heparin.

Streptokinase was more effective when the thrombus was in proximal rather than calf veins. Thrombi of more than six days old were readily lysed. Plasma fibrinogen levels were below 0·8 g/l (80 mg/100 ml) in nearly all patients successfully treated. The incidence of pulmonary embolism was no greater with streptokinase than with heparin treatment. Only prolonged follow-up would show whether thrombolytic treatment would be effective in preventing late complications of deep vein thrombosis such as chronic venous insufficiency.

Introduction

Early complete reopening of deep veins of the legs after thrombosis may preserve the valves and thus prevent the development of chronic venous insufficiency. We report here the treatment of 93 patients with streptokinase and compare the results with those in 42 patients treated with heparin. The effectiveness of thrombolytic treatment with streptokinase in preventing the late complications of deep vein thrombosis will be assessed by careful follow-up over many years.

Patients and Methods

Only patients with acute or subacute deep vein thrombosis confirmed by phlebography were considered for study. Those in whom there were no contraindications to thrombolytic therapy were treated with streptokinase followed by heparin and oral anticoagulants and the remainder with heparin and oral anticoagulants. From September 1962 to May 1972 145 patients were treated with streptokinase. In seven of these treatment was interrupted because of complications and in 45 a second phlebogram was either delayed or could not be made for technical reasons. Thus 93 patients whose progress was assessed by a repeat phlebography within 14 days after the start of streptokinase treatment remained for study. During the same period 42 patients considered unsuitable for thrombolytic treatment were treated with anticoagulants only. The two groups of patients were largely comparable in age, sex, and severity of their occlusions (tables I and II).

TABLE I—*Age in Years and Sex Distribution of Patients in Two Treatment Groups*

	Women		Men	
	Streptokinase	Heparin	Streptokinase	Heparin
10th percentile	21	45	32	41
50th percentile	46	72	59	56
90th percentile	71	81	72	76
No. of patients	33	15	60	27

TABLE II—*Types of Occlusion and their Distribution among 93 Patients Treated with Streptokinase and 42 Treated with Heparin. Results are Proportion of Patients*

	Streptokinase		Heparin	
	No.	%	No.	%
Adherent thrombus	37	40	14	33
Loose thrombus	11	12	7	17
Open veins	41	44	20	48
Not known	4	4	1	2

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Conditions regarded as absolute contraindications to thrombolytic treatment were a history of apoplexy or other cerebral accident less than two months before; manifest or recent gastrointestinal or other bleeding; the presence of hypertension, with a blood pressure persistently over 200/100 mm Hg or with a hypertensive retinopathy; subacute bacterial endocarditis; or metastasizing tumours. In no case was streptokinase treatment started until at least 10 days after the occurrence of bleeding, trauma, or an operation. Intramuscular injections were avoided.

THROMBOLYTIC TREATMENT

Streptokinase in 5% glucose solution for intravenous infusion was prepared twice daily to avoid loss of activity. The initial dose, given through a catheter in a cubital vein and injected slowly over 15-30 minutes in 20-ml glucose solution, was calculated according to the tolerance (see under Laboratory Tests) and plasma volume. The maintenance dose, infused at a rate of 30 ml/h, was two-thirds of the initial dose but did not exceed 100 000 U streptokinase^{-1}h^{-1}). The maintenance dose had sometimes to be modified when the lytic activity was inadequate as judged by fibrinogen concentration and euglobulin lysis time. In cases in which, after an initial rapid fall, the plasma fibrinogen level rose to over 0·8 g/l (80 mg/100 ml) heparin 15 000 to 20 000 U/24 h was given in addition while the dose of streptokinase was reduced to enhance the lytic activity since in nearly all cases an excess of streptokinase bound and inhibited either plasminogen or plasmin. The heparin infusion was continued so long as the plasma fibrinogen level remained over 0·8 g/l. To guard against possible allergic reactions prednisolone was given before the initial dose of streptokinase when this was 200 000 U or more. Prednisolone was also given in cases of allergic reaction during therapy.

Most patients were treated in the intensive care unit under constant supervision. Bleeding, especially at puncture sites, was carefully watched for and urine and faeces were inspected macroscopically for blood and the urine tested with Haemocombistix.

After stopping the streptokinase infusion heparin 10 000-20 000 U/h and oral anticoagulants were given when the plasma fibrinogen level reached 0·8 g/l. The maintenance dose was adjusted according to the thrombin time.

HEPARIN TREATMENT

Patients unsuitable for thrombolytic treatment were given an initial dose of heparin 5000 U followed by an infusion of 25 000 U/24 h. Further dosage was adjusted according to the thrombin time. Oral anticoagulation was started at the same time as heparin.

LABORATORY TESTS

The streptokinase tolerance, determined by the method of Fischbacher (1961), was defined as the number of streptokinase units required to lyse completely in 10 minutes at 37°C a clot obtained by recalcification of 1 ml of the patient's plasma. This number multiplied by the approximate plasma volume of the patient gave the initial dose of streptokinase.

The fibrinogen concentration and the inhibitory effect of the circulating fibrinogen or fibrin split products were assayed simultaneously by the method of Clauss (1957). The coagulation factors II, VII (Koller *et al.*, 1951), and X (Bachmann *et al.*, 1958) were assayed by previously described methods. Quick prothrombin times under heparin infusion were measured by the method of Seiler *et al.* (1970). The euglobulin lysis time was measured on euglobulin precipitated at pH 5·1-5·2 by acetic acid in distilled water and clotted by thrombin.

The thrombin time was measured, firstly, with a dilute thrombin solution (3-4 National Institutes of Health units/ml), giving a clotting time of 13-16 seconds with a normal plasma, and, secondly, with a concentrated solution (33 N.I.H.U/ml). Adequate heparinization gave a thrombin time of over two minutes with the diluted solution and of four to eight seconds with the concentrated one.

Results

The results of treatment were evaluated independently by an angioradiologist, an angiologist, and an expert in coagulation, who studied the phlebograms taken before and at a mean (± S.E. of mean) of 5·8 ± 2·5 days after the beginning of treatment. Treatment was rated (*a*) successful if the occluded veins were reopened along their whole length or at the point of strategic importance for the venous return—that is, the confluence of the superficial and the deep femoral veins and the great saphenous vein; (*b*) partially successful if reopening was incomplete; (*c*) unsuccessful if the phlebogram was unchanged; and (*d*) adverse if the occlusion had extended further. The ratings for thrombolytic and heparin are compared in table III.

TABLE III—*Results of Treatment in 93 Patients given Streptokinase and 42 given Heparin. Results are Proportion of Patients*

Treatment Rating	Streptokinase		Heparin	
	No.	%	No.	%
Successful	39	42	0	0
Partially Successful	23	25	4	10
Unsuccessful	30	32	37	88
Adverse	1	1	1	2

THROMBOLYTIC TREATMENT

Thrombolytic therapy was most effective when the thrombus was in the proximal rather than in the calf veins. Thus a successful rating was achieved in over half of the occlusions at strategic points compared with only one third of the occlusions of the popliteal and calf veins (table IV). Out of 117 veins with loose thrombi 54 (46%) were completely reopened during treatment. Out of 414 deep veins with adherent thrombi 128 (31%) were completely reopened. Apparently, so far as their age could be judged, thrombi of six to 15 days old, and sometimes older, were readily lysed (table V). Organized thrombi were not susceptible to thrombolysis.

TABLE IV—*Site of Occlusions and Success of Thrombolytic Treatment in 93 Patients treated with Streptokinase*

Occluded Vein	No. Occluded	No. (%) Completely Reopened
Iliac	12	12 (38)
Common femoral	53	35 (66)
Profunda femoris	52	29 (56)
Superficial femoral:		
proximal part	69	36 (52)
median part	63	26 (41)
distal part	68	26 (38)
Popliteal	68	22 (32)
Peroneal	77	25 (33)
Anterior tibial	80	18 (23)
Posterior tibial	85	24 (28)

TABLE V—*Delay in Starting Thrombolysis after First Symptoms and Effect on Result of Treatment*

Delay (Days)	No. of Patients	Treatment Rating			
		Successful (%)	Partially Successful (%)	Unsuccessful (%)	Adverse (%)
1	17	65	29	6	
2-3	23	43	10	43	4
4-5	20	15	30	55	
6-9	16	56	44		
10-15	10	50	10	40	
22-56	7	14	43	43	

The duration of thrombolytic treatment was about the same in all patients. The outcome of treatment did not depend on the streptokinase tolerance since the values in three groups of patients were not significantly different (table VI). Nevertheless, the tolerance was constantly higher in patients who needed heparin infusion in addition owing to reduced lytic activity. In 78 out of 93 patients the initial dose of streptokinase calculated from the tolerance test was equal to or lower than the lowest

TABLE VI—*Duration of Treatment and Streptokinase Tolerance in Three Groups of Patients*

Result of Treatment	Treatment	No. of Patients	Mean Duration of Treatment (h ± S.E. of Mean)	Mean Streptokinase Tolerance (U/ml plasma ± S.E. of Mean
Successful	Streptokinase	32	122·25 ± 29·2	43·8 ± 37·7
	Streptokinase + heparin	7	125·0 ± 30·5	88·1 ± 75·7
Partially successful	Streptokinase	21	102·5 ± 40·3	48·6 ± 33·3
	Streptokinase + heparin	2	149·5 ± 16·3	203·0 ± 50·9
Unsuccessful	Streptokinase	26	112·4 ± 23·2	67·2 ± 54·6
	Streptokinase + heparin	4	100·75 ± 39·2	106·8 ± 42·7

recommended standard initial streptokinase dose of 250 000 U streptokinase.

Thrombin times, plasma fibrinogen concentrations, and euglobulin lysis times were measured during treatment. Neither the euglobulin lysis nor the thrombin times bore any relation to the outcome. Fibrinogen levels, on the other hand, were lower in patients in whom treatment was successful, nearly all being below 0·8 g/l (table VII). Treatment was never successful in patients whose fibrinogen level remained above 0·8 g/l after the first 48 hours of therapy. For that reason patients treated during the later part of the period under review who had fibrinogen levels of this order were always given heparin in addition to streptokinase.

TABLE VII—*Mean Plasma Fibrinogen Levels (g/l ± S.E. of Mean) during Thrombolysis related to Result of Treatment*

Result of Treatment	Day 0	Day 1	Day 3
Successful	3·8 ± 1·31	0·36* ± 0·1	0·5* ± 0·2
Successful with addition of heparin	3·91 ± 1·07	0·33 ± 0·09	1·10 ± 0·26
Unsuccessful	4·57 ± 2·07	0·52 ± 0·32	0·85 ± 0·74
Unsuccessful with addition of heparin	6·85 ± 0·74	0·88* ± 1·15	1·67* ± 0·66

* Difference was significant ($P<0·01$) only between treatments successful without heparin and treatments unsuccessful with addition of heparin.

HEPARIN TREATMENT

In the 42 patients treated with only heparin and oral anticoagulants the average interval between the start of treatment and the second control phlebogram was 6·7 ± 3·4 days. Treatment was in no case successful, but in four it was partially so. The phlebogram remained unchanged in 37 cases and showed an additional occlusion in one case (table III). Heparinization was sufficient in all but 10 (24%) patients. In these the thrombin times were less than 60 seconds in more than two-thirds of the daily tests. The smallest daily dose of heparin was 20 000 IU.

SIDE EFFECTS

The incidence of pulmonary embolism was no greater during thrombolytic treatment than during heparinization (table VIII). Other side effects were commoner and severer in patients treated with streptokinase. Specific complications were bleeding due to the drug's fibrinolytic action on haemostatic clots and allergic manifestations due to its antigenic properties. Phlebitis at the infusion site was common with streptokinase and rare with heparin. Two patients had no control phlebogram after streptokinase treatment because they died—one of pulmonary embolism, the other of paradoxical embolism.

TABLE VIII—*Side Effects in 93 Patients treated with Streptokinase and in 42 treated with Heparin. Results are Proportion of Patients*

Side Effects	Streptokinase		Heparin	
	No.	%	No.	%
None	11	11·8	36	85·7
Pyrexia ≤ 38°C and/or Hb loss < 20 g/dl	58	62·4	4	9·5
Pyrexia > 38°C and/or Hb loss 20 g/dl	24	25·8	2	4·8
Pulmonary embolism	7	7·5	5	11·9

Discussion

Our finding that thrombolysis with streptokinase totally or partially clears occluded veins in 67% of cases compared with 10% of heparin-treated patients corresponds with those of others in studies of fewer patients (Browse *et al.*, 1968; Kakkar *et al.*, 1969 a; Robertson *et al.*, 1970; Jacobsen, 1973).

Success in treatment depends on the age, site, and size of the thrombus. Even though, according to Schmitt (1975), loose thrombi are more recent than adherent ones a good prognosis can never be made on the evidence of the phlebogram. It can merely be established that proximal veins, important for venous return, are more often reopened than distal ones, possibly because the occlusions are usually more recent. Though the age of the thrombus is important it is less so than was at first thought. Streptokinase treatment used to be reserved for acute thromboses. Such a limitation is unjustifiable since it is not certain that the valves suffer permanent damage after several days of occlusion, as postulated by Kakkar *et al.* (1969 b). Only a follow-up of cases will show whether a relatively late reopening of the veins can prevent subsequent chronic venous insufficiency.

Rethrombosis, observed by others (Dhall *et al.*, 1973; Mavor *et al.*, 1973), occurred on only one of our cases, probably because the individual dosage of streptokinase made it possible to maintain the fibrinogen at a constantly low level. We prefer a dosage based on the tolerance test and laboratory assays because, firstly, for the same lytic action the dose is usually smaller and thus more economical (and also possibly reducing the risk of side effects), and, secondly, the fibrinolytic action can be varied according to the laboratory findings. The latter is particularly important. In the past we had no criteria to guide treatment. During the course of this study we found that successful thrombolysis was related to the fibrinogen level, and that treatment was unsuccessful when plasma fibrinogen was above 0·8 g/l (Duckert *et al.*, 1974). When the plasma fibrinogen could not be reduced below this level heparin was given in addition. The required degree of anticoagulation was achieved and in some cases the fibrinolytic treatment became successful.

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