THROMBOLYTIC THERAPY
IN
VENOUS THROMBOEMBOLISM

MEDICAL GRAND ROUNDS

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THROMBOLYTIC THERAPY FOR
VENOUS THROMBOEMBOLISM

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A. HISTORY

1. Streptokinase

In 1933 Tillett and Garner noted that a filtrate of Beta-hemolytic streptococci caused the rapid liquefaction of human plasma coagulum. Ten years later Christensen and McLeod (1945) demonstrated that the streptococcus produces an activator substance which acts on plasminogen to form the active enzyme plasmin. The efficacy of streptokinase in promoting in vivo lysis of thrombi was first demonstrated in animals by Johnson and Tillett (1952) and in humans by Johnson and McCarthy (1959). Alkjaersig, Fletcher and Sherry (1959) reported on the mechanism of clot dissolution by plasmin and demonstrated that streptokinase could induce and maintain a sustained thrombolytic state in man.

2. Urokinase

Because of the antigenic and pyrogenic problems of streptokinase a more ideal plasminogen activator was sought. Urokinase had been known since the observation by MacFarlane in 1947 of the in vitro thrombolytic capability of urine. Ploug and Kjeldgaard reported a method of isolating urokinase from urine and described its properties (1957). The same group (Hanson et al, 1961) reported experiences with intravenous urokinase in humans.

B. GENERAL REVIEWS

Good general reviews are available on the subject of streptokinase (Brogden et al, 1973), urokinase (Paoletti and Sherry, 1977) and thrombolysis in general (Fratantoni et al, 1975; Verstraete, 1978; and Kakkar and Scully, 1978).

C. MECHANISM OF ACTION

1. Streptokinase

A large number of studies elucidating the mechanism of action of streptokinase has been summarized by Brogden et al (1973). Streptokinase is a single chain protein with molecular weight of 47,000 Daltons. Streptokinase itself has no enzymatic activity. Streptokinase combines with plasminogen to form a complex. The complex serves as the activator to convert other plasminogen molecules to plasmin. Streptokinase appears to induce a confirmational change in the structure of plasminogen so that an active site is exposed. With time the streptokinase plasminogen complex is gradually converted to streptokinase-plasmin form which also has the ability to activate plasminogen.

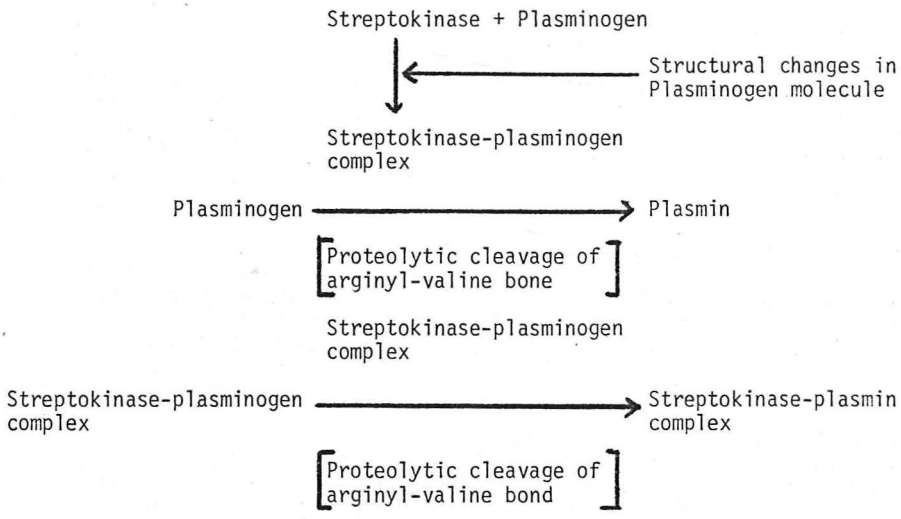


FIGURE 1. Diagramatic representation of the activation of plasminogen by streptokinase.

Maximum activator is formed when streptokinase and plasminogen are present in a 1:1 molar concentration. Maximum plasmin formation is generated when the streptokinase molar concentration is approximately 10% of the plasminogen concentration. Therefore, the addition of small amounts of streptokinase to a given quantity of plasminogen will produce a high level of plasmin, while a high concentration of streptokinase will produce little plasmin and a high level of the activator complex.

2. Urokinase

Urokinase is a β-globulin, a single polypeptide chain with a molecular weight of 54,000. The activation of plasminogen to plasmin by urokinase is not a simple one-step action. One possible series of events succinctly summarized by Kakkar and Scully (1978), is shown in Figure 2.

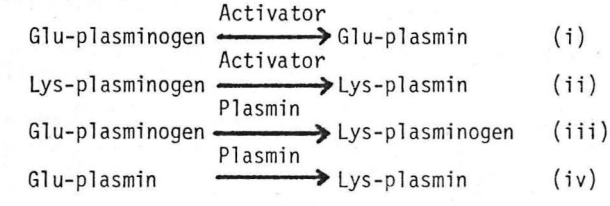


FIGURE 2. Peptide bond cleavage during activation of plasminogen.

If some plasmin is formed, the native plasminogen (glu-plasminogen) is degraded slightly to a plasminogen with lysine as the N-terminal amino-acid. This lys-plasminogen has more of a tendency to adhere to fibrin and is activated more rapidly to plasmin (Thorsen 1975; Thorsen and Mullertz, 1974). Urokinase is different from tissue activator. Tissue activator has a much stronger tendency to bind to fibrin and is more uniformly inhibited by epsilon-aminocaproic acid (EACA) (Thorsen et al 1974b, Thorsen et al, 1972).

The urokinase used in the Urokinase Pulmonary Embolism Trial was concentrated from human urine. The commercially available urokinase from Abbott Laboratories is produced by embryonic kidney cell cultures and is identical to urokinase concentrated from urine. One cannot help but wonder if cell culture techniques could produce tissue activator which has potential advantages over urokinase.

3. Plasminogen

Plasminogen is a single chain molecule with a molecular weight of 93,000 daltons. In fresh human blood plasminogen occurs in several molecular forms, all with aminoterminal glutamic acid. Aminoacid sequence of plasminogen, showing three distinct regions of interest, have been summarized by Kakkar and Scully (1978).

1. A small segment of about 75 aminoacids at the N -terminal end of the molecule is released during the formation of lys-plasminogen.

2. The central portion of the molecule contains lysine binding sites and may be involved in the absorption of plasminogen by fibrin.

3. The C terminal part of the molecule has been shown to contain the serine residue essential for enzyme activity.

4. Plasmin has a trypsin-like activity hydrolysing proteins and peptides at arginyl and lysyl peptide bonds and also hydrolysing basic aminoacid esters and amides. Plasmin can also activate factor XII (Hageaman factor) and hence influence the coagulation, Kallikrein- kinin and complement systems. Plasmin digest either fibrinogen or fibrin into progressively smaller fragments X, Y, D and E. Prothrombin, factors V and VIII are also digested by plasmin (Verstraete, 1978).

5. Mechanism of Thrombolysis

Evidence exists for at least three mechanisms of thrombolysis and probably all three exist to some extent.

a. Plasmin-antiplasmin complex. There is evidence that antiplasmin complexes with plasmin in solution and prevents lysis of fibrinogen. However, plasmin has greater affinity for fibrin than for the antiplasmin and dissociates in the presence of a fibrin clot leading to lysis of the fibrin (Mullertz, 1952; Celander and Guest, 1957; and Ambrus and

Marcus, 1960)

b. Plasminogen incorporated within the clot becomes activated by means of activators diffusing into the clot. Sherry et al, (1959a) proposed the concept of lysis from within the clot by this mechanism. Plasminogen has been found to be actually more concentrated in the clot than in plasma (Scully et al, 1973).

c. Activator binds to the surface of the clot and activates circulating plasminogen. Lysis of retracted clot soaked in streptokinase and washed increases markedly with increasing concentrations of plasminogen in the surrounding media (Gottlob and Blumel, 1968). Streptokinase absorbed on thrombi causes more lysis when the thrombi are perfused with fluid containing plasminogen than with fluid containing more streptokinase (Chesterman et al, 1972).

D. DOSAGE AND METHOD OF ADMINISTRATION

1. Streptokinase

a. Loading dose

The major purpose of the loading dose is to neutralize antistreptococcal antibodies that cross react with streptokinase. It is desirable to have enough excess streptokinase to complex most of the plasminogen in the plasma to form an activator. Unless most of the plasminogen is complexed with streptokinase there will be a large amount of plasminogen available to be activated to plasmin. If enough plasmin is formed it can exceed the inhibiting capacity of the antiplasmins available and produce substantial lysis of fibrinogen rather than fibrin.

Ideally the loading dose of streptokinase is a titrated initial dose (T.I.D.). It is calculated by multiplying an assumed plasma volume by the streptokinase resistance. The streptokinase resistance is determined by finding the minimal number of units of streptokinase producing lysis of a 1 ml plasma clot in 10 minutes at 37 degrees centigrade (Mavor et al, 1969). A commercially available kit called the Streptokinase Resistance Test Reagent is available from Behring Diagnostic Laboratories which is part of Hoechst Pharmaceuticals. There are difficulties with reproducibility of the streptokinase resistance test (Amery et al, 1962) and a standard loading dose is frequently used. From the available literature it can be predicted that the titrated initial dose will be less than 1,250,000 units in 97% of the population (Verstraete et al, 1966), less than 600,000 units in 95% of the population (Olow et al, 1970) and less than 250,000 units in approximately 90% of patients. If the loading dose is insufficient to neutralize the streptococcal antibodies in a patient, it would be predicted that excess circulating plasminogen would be available to be converted to plasmin. Hyperplasminemia could result in marked fibrinogen depletion, marked elevation of fibrin degradation products and a great tendency to bleeding. However, Hirsh et al (1970) used a standard loading

dose of 250,000 units and in the 4 patients who had greater streptokinase resistance and no bleeding occurred; lysis was slightly delayed but adequate. There is also a theoretic disadvantage of using too large a dose. If rethrombosis occurred during plasminogen depletion the clots would be resistant to lysis (Brogden et al, 1973). The Urokinase Streptokinase Embolism Trial (1974) utilized a standard loading dose of 250,000 units and this dose is recommended by manufacturers of Streptase. It is recommended that this dose be given intravenously over a 30 minute period followed by a sustaining maintenance dose for the next 72 hours.

b. Numerous studies have shown a maintenance dose of 100,000 units per hour to be satisfactory. A duration of 24 hours for pulmonary embolism and 72 hours for deep venous thrombosis is recommended. Preliminary studies with lower doses and shorter periods of treatment showed poor lysis in deep venous thrombosis (Robertson et al, 1970). The maintenance dose is adjusted by following a plasma thrombin time. It is usually expected to be greatly prolonged the first 4 hours after the bolus infusion. After 12 hours, if the thrombin clotting time is more than 5 times the control thrombin clotting time, too much plasminogen is being converted to plasmin and not enough of the plasminogen is being complexed as an activator with streptokinase. Under these circumstances of too much effect, paradoxically, it is recommended that the dose of streptokinase be increased to bind more of the plasminogen as activator and have less available to be converted to plasmin. The dose of streptokinase should be doubled at 4-hour intervals until the ratio of the thrombin clotting time to control falls in the range of 2:1 to 5:1 or a maximum of a million units per hour is reached. Similarly, if the thrombin time falls to less than 2 times the control, the hourly dose of streptokinase should be halfed at 4-hour intervals until the ratio of the thrombin time to control was in the desired range of 2:1 to 5:1 or until a minimum dose of 100,000 units per hour is reached. It is recommended that heparin be started approximately 2 hours after discontinuance of streptokinase, after the thrombin clotting time dropped to less than 2 times the control (Seaman et al, 1976).

The contraindications to streptokinase or urokinase therapy are listed in Table I.

TABLE I. Contraindications for Streptokinase Therapy

Hemorrhagic diathesis
Recent history of peptic ulcer disease
Severe systemic hypertension
Cerebral vascular accident within the previous 6 months
Suspected carotid artery thrombosis
Atrial fibrillation
Recent streptococcal infection
Active tuberculosis
Severe liver disease with bleeding diathesis
Renal failure
Pregnancy and postpartum period (10 days)
Surgery within the previous 10 days
Hepatic or renal biopsy within the previous 10 days
Translumbar aortography within the previous 14 days

2. Urokinase

a. Loading Dose

The standard loading dose used by the Urokinase Pulmonary Embolism Trial (1973) and recommended by Sherry (1976) is 2,000 CTA units per pound of body weight given intravenously over a 10 minute period.

b. Maintanance Dose

1. Sustaining intravenous infusion of 2,000 CTA units per pound of body weight per hour for periods of 12 to 24 hours is recommended for pulmonary embolism. Monitoring of urokinase dose with thrombin clotting times is not considered essential.

3. The cost of 12 hours worth of urokinase is about $3000.00 and 24 hours worth of streptokinase costs about $200.00. It becomes a judgement matter to decide whether the cost difference justifies the advantages of urokinase. Urokinase is non-pyrogenic, non-antigenic and has preferential affinity for gel-phase plasminogen.

E. LABORATORY CONTROL OF TREATMENT.

The only laboratory test that is considered essential is a thrombin clotting time if streptokinase is used. This is used to alter the dose of the maintenance infusion as indicated above.

The Urokinase Streptokinase Embolism Trial (Bell, 1975) measured plasma fibrinogen, plasminogen, euglobulin lysis times and fibrinogen/fibrin degradation products. There was mild to moderate lowering of fibrinogen and plasminogen with urokinase and a more dramatic lowering with streptokinase. With streptokinase the fibrinogen levels were reduced from approximately 500 mg/100 ml to approximately 150 mg/100 ml and plasminogen was reduced from about 2½ units per ml to less than .2 units per ml. Also the euglobulin lysis time was shorter and the fibrinogen/fibrin degradation products higher with streptokinase. The results of these studies were not reported to be beneficial in terms of predicting degree of lysis or bleeding complications. Marder et al (1977) evaluated streptokinase in acute deep venous thrombosis and also found no correlation of the degree of lysis with laboratory test results. Two uncontrolled studies, one in pulmonary embolism (Schwartz et al, 1973) and one with ileofemoral deep venous thrombosis (Mavor et al, 1973) attributed thrombo-embolic complications or re-thrombosis after the streptokinase treatment to marked depletion of plasminogen and only minor decreases in fibrinogen concentrations.

F. FACTORS THAT INFLUENCED THE RATE OF LYSIS.

1. Amount of plasminogen in the thrombus or in plasma.

If plasminogen is deficient in the thrombus or the plasma, lysis will not be good. (Alkjaersig et al, 1959; Chesterman et al, 1972)

2. The age of the thrombus or embolus.

Experimentally, older pulmonary emboli have been found to lyse less well (Wolf and Genton, 1967). The poor lysis has been attributed to more cross-linking of fibrin. More recent studies with in vitro clots found that the degree of cross-linking did not influence the rate of fibrinolysis by streptokinase and urokinase (Rampling, 1978).

Poor lysis of older clots in experimental animals and humans may be more related to the ingrowth of fiberblasts and collagen fibers than to the amount of cross-linking of fibrin. The presence of fibroblasts and collagen fibers has been demonstrated in the thrombus on the fifth day (Kakkar and Scully, 1978). Some studies report much better lysis of deep venous thrombosis if the symptoms have been less than 3 or 4 days (Kakkar et al, 1969) and others report poor lysis of older thrombi (Astedt et al, 1974). However, some investigators found that the age of the thrombus did not necessarily predict how well it would lyse (Mavor et al, 1973). Duckert et al (1975) reported that deep venous thrombi more than 6 days old were readily lysed.

Chronic pulmonary thromboembolism was not benefited by streptokinase therapy. (Miller et al, 1969).

3. Delivery of the thrombolytic agent to the site of the thrombus or embolus.

Thrombolytic therapy is likely to be ineffective if deep venous thrombi completely occlude a vein (Browse et al, 1968) or if massive pulmonary emboli completely occlude pulmonary artery branches and are associated with a very marked decreased capillary filling phase on the angiograms (Tibbutt et al, 1974).

In experimental occlusive femoral vein thrombosis in dogs ^{131}I-plasminogen localizes in the distal end of the thrombus up to 10 times more than in the proximal end. Perhaps lysis occurs only at the distal end of an occlusive thrombus (Scully et al, 1974).

G. CLINICAL STUDIES

1. Deep venous thrombosis

a. Uncontrolled clinical trials

The results of intravenous streptokinase therapy for acute deep venous thrombosis are summarized from 13 studies from 1967 through 1977 in Table 2. 292 patients were treated with streptokinase. 103 (35%) had complete lysis demonstrated on repeat phlebography. 103 (35%) had partial lysis demonstrated on follow up phlebograms and 85 (29%) had little or no improvement or some worsening on repeat phlebograms. Four patients did not have follow up phlebograms. This is in contrast with the results of intravenous heparin

TABLE 2. RESULTS OF INTRAVENOUS STREPTOKINASE THERAPY FOR ACUTE DEEP VENOUS THROMBOSIS (NON-RANDOMIZED TRIALS)

AUTHOR	NO OF PATIENTS	AGE OF THROMBUS	PHLEBOGRAPHIC IMPROVEMENT			DOSAGE		DURATION OF THERAPY	MAJOR BLEED
			COMPLETE	PARTIAL	NIL	LOADING	MAINTENANCE		
Gormsen et al 1967	14	<7 days	4	4	6	T.I.D.	2/3 T.I.D. per hour	5 days (average)	2
Browse et al 1968	5	3 < 7 days 2 < 21 days		4	1	600,000u	100,000u per hr	3 days	
Kakkar et al 1969	10	8 < 3 days 2 < 14 days	4	4	2	500,000 u	100,000 u to 150,000 u/hr	<7 days	1
Mavor et al 1969	10	<3 days Rethrombosis after thromb-ectomy	2	7 (5 marked)	1	T.I.D.	750,000 u in 4 hr & then q 8 hr	16-52 hours	1
Olow et al 1970	13	12 < 4 days 1 was 16 days	6	2	2	600,000 u	100,000 u/hr	<4 days	2
Robertson et al 1970	8	< 5 days	8	0	0	T.I.D. x 2	100,000 u per hr	3 days	
Diaz et al 1971	10	NS	2	8	0	250,000 u	100,000 u per hr	3 days	
Mavor et al 1973	39 ileofem-oral	NS	10	24	5	T.I.D.	750,000 u in 4 hr & then q 8 hr	7-83 hours	
Aesdt et al 1974	33 8	< 5 days > 5 days	10	19	4 8	250,000 u	100,000 u/hr	3 days	2

TABLE 2 (CONTINUED)

AUTHOR	NO OF PATIENTS	AGE OF THROMBUS	PHLEBOGRAPHIC IMPROVEMENT			DOSAGE		DURATION OF THERAPY	MAJOR BLEED
			COMPLETE	PARTIAL	NIL	LOADING	MAINTENANCE		
Duckert et al 1975	93	60 < 6 d up to 56 days "successful"	39	23	31	T.I.D.	2/3 T.I.D. up to 100,000 u/hr	4 days	
Johansson et al 1976	19	10 < 7 days 9 > 7 days	7	4	7	600,000 u	100,000 u/hr	36-96 hours	3
Norgren et al 1977	14	1-10 days	5	2	5	600,000 u	100,000 u/hr	72 hr	
Baker et al 1977	16	9 < 7 d 7 were 9-20 days	1	2	13	600,000 u	100,000 u/hr or 300,000 u/hr bolus	3 days 3-5 days	
TOTAL	292		98	103	85				11

NS = Not Stated T.I.D. = Titrated Initial Dose

therapy in 3 studies summarized in Table 3. A total of 61 patients were studied and only one of these had complete lysis on repeat phlebography. 7 (11%) had partial and 49 (80%) had poor or no lysis on repeat phlebography. Four patients did not have repeat phlebography. 69% of patients treated with streptokinase had complete or partial lysis, whereas only 13% of patients treated with heparin had complete or partial lysis on repeat phlebography.

Five of the studies utilizing intravenous streptokinase based the loading dose on a titrated initial dose (T.I.D), related to the amount of streptococcal antibodies present in the patient's plasma. The results in these studies were no better than studies utilizing a standard loading dose of 250,000 to 600,000 units of streptokinase, except for the study of Robertson et al (1970). These authors attributed their excellent results to starting therapy within 5 days of the onset of symptoms in all 8 patients. Aesdt et al, found consistently poor results in 8 patients treated more than 5 days after the onset of symptoms. However, in general, most of the authors found that the duration of symptoms did not predict their degree of lysis with streptokinase.

b. Controlled clinical trials.

The results of 6 randomized controlled trials comparing intravenous streptokinase and anticoagulants for deep venous thrombosis are summarized in Table 4. The results are similar to the uncontrolled trials. A total of 92 patients treated with streptokinase had follow up phlebography usually within 4 to 10 days. There was complete lysis in 22 (24%), partial lysis in 31 (34%) and little or no lysis in 31 (34%). Eight patients did not have follow up phlebograms. Patients randomized to treatment with intravenous heparin showed complete lysis in only 3 (4%) and partial lysis in 17 (24%). The results with ancrod were similar. There was partial or complete lysis with streptokinase in 58% of the patients, compared to only 27% of the patients treated with either heparin or ancrod.

Some authors found better lysis if the thrombus was located more proximally in the leg (Marder et al, 1977). Mavor et al (1973) found average results in iliofemoral deep venous thrombosis, but Baker et al (1977) had very poor results with extensive iliofemoral thrombosis.

The only evaluation of urokinase in deep venous thrombosis (Sharma et al, 1977) was an analysis of some of the patients in the Urokinase Streptokinase Pulmonary Embolism Trial. Patients who had abnormal impedance plethysmography had follow up at 24 hours and 7 days. Only 25% of the patients treated with heparin had resolution, whereas 73% of the patients treated with Urokinase had resolution and almost all of these resolved within 24 hours.

TABLE 3. RESULTS OF INTRAVENOUS HEPARIN THERAPY FOR ACUTE DEEP VENOUS THROMBOSIS (NON-RANDOMIZED TRIALS)

AUTHOR	NO OF PATIENTS	AGE OF THROMBUS	PHLEBOGRAPHIC IMPROVEMENT			DOSAGE		DURATION OF THERAPY	MAJOR BLEED
			COMPLETE	PARTIAL	NIL	LOADING	MAINTENANCE		
Gormsen et al 1967	14	12<3 days 2<7 days	1	2	7	12,000u SC	12,000u SC q 12 hr	NS	NS
Browse et al 1968	5	2<7 days 3<21 days		1	4	5,000u	5,000u I.V. q 4-6 hr	48 hr + warfarin	NS
Duckert et al 1975	42	NS		4	38		20,000u + per day	NS	NS
TOTAL	61		1	7	49				

N.S. = NOT STATED

TABLE 4 RANDOMIZED CONTROLLED TRIALS COMPARING INTRAVENOUS STREPTOKINASE AND ANTICOAGULANTS FOR ACUTE DEEP VENOUS THROMBOSIS

AUTHOR	NO OF PATIENTS	AGE OF THROMBUS	PHLEBOGRAPHIC IMPROVEMENT			DOSAGE		DURATION OF THERAPY	MAJOR BLEED
			COMPLETE	PARTIAL	NIL	LOADING	MAINTENANCE		
Kakkar et al	10 S	< 4 days	6	1	2	500,000u	900,000 6 hr	6 days	3
1969	10 H		2	2	5	10,000u	10,000-15,000 q 6 hour		2
	10 A		1	3	6	80 u x 2	40-80 u q 6 hr	5+ days	0
Robertson er al	9 S	< 5 days	3	2	4	TID x 2	100,000 u/hr	3 days	
1970	7 H		0	1	6	7,500 u	2,000 u/hr	3 days	
Tsapogas et al	19 S	< 5 days	3	7	9	100,000-500,000u Based on T.I.D.	100,000 u per hr	1-3 days	3
1973	15 H			1	14	7,000u	1500 u/hr	7 days	
Tibbutt et al	18 S	5 > 7 days	4	11	2	600,000u	100,000 u/hr	4 days	1
1974	16 A	4 > 7 days	0	2	13	140 u	70 u q 2 hr	4 days	0
Seaman et al	24 S	< 14 days	6	5	10	250,000u	100,000 u/hr	3 days	4
1976	26 H	< 14 days	1	10	14	150 u/kg	1000-1500 u/hr	10 days	1
Marder et al	12 S	1-20 days		5	4	250,000u	100,000 u/hr	3 days	4
1977	12 H	1-14 days		3	9	150 u/kg	Continuous	7 days +	1

Note: All patients were placed on warfarin following intravenous therapy

S = Streptokinase H = Heparin A = Ancrod

c. Preservation of venous valve function

There are very few studies that have done careful long term follow-up after streptokinase therapy. Most of the studies that attempt follow-up lump patients treated with streptokinase and anticoagulants into groups according to the amount of lysis observed during acute treatment. Most of the patients that have complete lysis during the acute treatment fall into the streptokinase therapy. Summary of four such studies is included in Table 5. A total of 31 patients had phlebographic follow-up from 1 to 12 months after acute treatment. 29 of the patients still had complete phlebographic patency. It appeared not to make much difference whether long term anticoagulation was used. Kakkar et al (1969) evaluated venous valve function with ascending cinephlebography and found that 5 of the 8 patients with completely patent channels had normally functioning venous valves. In all of these instances where valvular function returned to normal, the diagnosis had been made early within 36 hours of the onset of thrombosis and the thrombi had cleared rapidly within 72 hours of the beginning of treatment as judged by phlebography.

The patients who had only partial lysis of acute deep venous thrombosis evaluated by phlebography at the end of streptokinase or anticoagulation treatment have also been evaluated in follow-up 4 to 12 months later. A total of 43 patients have been studied by four groups summarized in Table 6. Nine patients at follow-up showed complete lysis and patency of the venous channels. Seven of these had received long term anticoagulation for 6 to 12 months. 13 patients showed re-thrombosis at the time of follow-up at phlebographic evaluation. 12 of these patients had received no anticoagulation following streptokinase. These patients also had extensive iliofemoral thrombosis initially and some of them had rethrombosed following attempt at thrombectomy before treatment with streptokinase. It appears that thrombosis is likely to recur if initial lysis has only been partial and long term anticoagulation is not given. If lysis is only partial acutely and long term anticoagulation is given, complete lysis may eventually result. However, in Kakkar's experience (1969) none of the 8 such patients had normal venous valve function on cinephlebography. It is not known whether it would be better to have a completely patent channel with destroyed valve function or whether it would be better to have a partially recanalized venous channel. The presence or absence of swelling or pain in the extremities of the patients in Table 6 were commented upon in only one patient who had complete recannulization and had no symptoms. In the randomized study reported by Tibbutt et al (1974) 15 of 18 patients treated with streptokinase had complete or substantial lysis when evaluated immediately following treatment. However, at 3 months, only 1 of the patients had a normal limb.

In a retrospective study Bieger et al (1976) evaluated 51 patients 31-47 months after treatment of clinically diagnosed deep venous thrombosis with heparin and/or phenprocoumon. Phlebograms showed residual thrombi in all patients. Sixteen had residual thrombi above the knee and 9 (56%) of these had severe post thrombophlebic syndrome. Thirty-five had residual thrombi confined to the calf and only 3 (9%) of these had severe post thrombophlebitic syndrome. In a small prospective study the same authors (Bieger et al, 1976) found the results of heparin therapy to be inferior to streptokinase but better than home treatment with phenprocoumon orally.

TABLE 5. LATE VENOGRAPHIC FOLLOW-UP OF PATIENTS WITH INITIAL COMPLETE LYSIS OF ACUTE DEEP VENOUS THROMBOSIS

AUTHOR	TIME OF FOLLOW UP	NO OF PATIENTS	CLINICAL		PHLEBOGRAPHIC PATENCY			FOLLOWED BY	
			SWELLING	PAIN	COMPLETE	PARTIAL	NIL	IN PT HEPARIN	OUT PT ORAL ANTI-COAGULANT
Mavor et al 1973	4 mos	10	NS	NS	8		2	No	No
Olow et al 1970	1-10 mos	6	1	0	6			Yes	No
Johansson et al 1969	6-50 mos	7	0	0	7			Yes	Usually 3-6 mos
Kakkar et al 1969	6-12 mos	8	NS	NS	8(5)			No	No
TOTAL		31			29		2		

NS = NOT STATED ( ) = NORMAL VALVE FUNCTION

TABLE 6. LATE VENOGRAPHIC FOLLOW-UP OF PATIENTS WITH INITIAL PARTIAL LYSIS OF ACUTE DEEP VENOUS THROMBOSIS

AUTHOR	TIME OF FOLLOW UP	NO OF PATIENTS	CLINICAL		PHLEBOGRAPHIC PATENCY			FOLLOWED BY	
			SWELLING	PAIN	COMPLETE	PARTIAL	NIL	INPATIENT HEPARIN	OUTPATIENT ORAL ANTI-COAGULANT
Mavor et al 1973	4-6 mos	24	NS	NS		12	12	No	No
Olow et al 1970	4 mos	1	0	0	1			Yes	No
Johansson et al 1976	6-50 mos	4	NS	NS		3	1	Yes	Usually 3-6 mos
Kakkar et al 1969	6-12 mos	8	NS	NS	7(0)	1		No	6-12 mos
		6	NS	NS	1(0)	5			No
TOTAL		43			9	21	13		

NS = NOT STATED ( ) = NORMAL VALVE FUNCTION

Some studies report the findings of late follow-up venograms according to whether the patient was initially treated with streptokinase or initially treated with heparin rather than according to the initial result. Such a study is that of Rösch et al (1976) and the findings are summarized in Table 7. Normal venographic findings with preservation of valves were present in 6 of 15 treated with streptokinase and in only 1 of 12 with heparin.

Venous valve function has been evaluated by a plethysmographic technique in 14 patients treated with streptokinase and followed up 8 to 53 months after the treatment (Norgren et al, 1977). Of the 14 patients evaluated, 8 had complete recovery by clinical evaluation. Five had complete recovery by initial phlebographic follow-up, but only 3 of these had normal venous function evaluated by plethysmography.

TABLE 7

VENOGRAPHIC FINDINGS IN LATE FOLLOW-UP STUDIES OF PATIENTS WITH ACUTE DEEP VEIN THROMBOSIS

	STREPTOKINASE	HEPARIN
NORMAL	6	1
SEGMENTAL VALVE PRESERVATION	1	1
COMPLETE RECANALIZATION	4	7
PARTIAL RECANALIZATION	4	3
TOTAL	15	12

RÖSCH ET AL AM J RADIOL, 1976

2. Pulmonary embolism

a. Uncontrolled trials

The results of treatment of major and massive pulmonary embolism with streptokinase are summarized in Table 8. The patients all had pulmonary embolism documented and the amount of resolution evaluated angiographically after 12 to 72 hours of streptokinase therapy. 54 (77%) of the total of 70 patients had marked to moderate resolution on the repeat pulmonary angiogram. This is in sharp contrast to 32 similar patients treated with heparin and evaluated with repeat pulmonary angiograms 17 to 72 hours later Table 9. None of the patients treated with heparin had marked to moderate resolution on the repeat pulmonary angiogram.

TABLE 8. TREATMENT OF MAJOR AND MASSIVE EMBOLISM WITH STREPTOKINASE (NON-RANDOMIZED TRIALS)

AUTHORS	NO OF PATIENTS	AGE OF EMBOLUS (CLINICAL)	DOSAGE OF STREPTOKINASE	DURATION OF THERAPY	ANGIOGRAPHIC RESOLUTION		PULMONARY EMBOLECTOMY	DEATHS	MAJOR BLEEDS
					MARKED TO MODERATE	MINIMUM OR NIL			
Hirsh et al (1967)	1	? approx. 24 hours	TID load;100,000u hourly + heparin	24 hours	1	0	0	0	0
	1	24 hours	25,000u load;12,500-20,000u hourly + heparin	24 hours	1	0			
Hirsh et al (1968)	15 3	5-48 hrs 16-40 days	TID load; 20,000-200,000u per hr maintenance	9-60 hours usually 24 hours	11	4	2	2	3
Chesterman et al (1969)	4	<24 hours	250,000u load; 100,000u hourly	5-40 hours	1	0	0	1	
Miller et al (1969)	4	12 hours -6 days	600,000u load; 100,000u hourly	36 hours	4	0	0	0	3
Miller et al (1971)	15	2-48 hours	600,000u load; 100,000u hourly	72 hours	13	2	0	0	
Hirsh et al (1971)	22	4-72 hours	TID load; 100,000u hourly	24 hours	19	2	2	0	3
Diaz and Leveen (1971)	1	NS	250,000u load; 100,000u hourly	72 hours	1	0	0	0	

TABLE 8. (CONTINUED)

AUTHORS	NO OF PATIENTS	AGE OF EMBOLUS (CLINICAL)	DOSAGE OF STREPTOKINASE	DURATION OF THERAPY[1]	ANGIOGRAPHIC RESOLUTION		PULM-ONARY EMBO-LECTOMY	DEATHS	MAJOR BLEEDS
					MARKED TO MOD-ERATE	MINIMUM OR NIL			
Strickland et al (1973)	1	48 hours	500,000u load; 100,000 hourly	28 hours	1	0	0	0	0
Schwartz et al (1873)	3	36-80 hours	TID load;200,000-100,000u hourly	12-17 hours	2	1	0	1(2 days after stopping SK)	
TOTAL	70				54	9	4	3	9

[1] DURATION OF THERAPY UNTIL SECOND PULMONARY ANGIOGRAM.

ABBREVIATIONS: TID = TITRATED INITIAL DOSE. SK = STREPTIKONASE. NS = NOT STATED.

TABLE 9. TREATMENT OF A MAJOR AND MASSIVE EMBOLISM WITH HEPARIN IN NON-RANDOMIZED TRIALS

AUTHORS	NO OF PATIENTS	AGE OF EMBOLUS (CLINICAL)	DOSAGE OF HEPARIN	DURATION OF THERAPY[1]	ANGIOGRAPHIC RESOLUTION		PULMONARY EMBOLECTOMY	DEATHS	MAJOR BLEED
					Marked To Moderate	Minimal to Nil			
Hirsh et al (1967)	1	? Approx. 2 hours	NS	24 hours	0	1	0	0	
Hirsh et al (1971)	10	5-48 hours	10,000u load; 30,000u per 24 hours	24 hours	0	10	0	0	NS
Miller et al (1971)	8	2-48 hours	40,000-60,000u per 24 hours	72 hours	0	6	1	0	1
McDonald et al (1971)	9	5-48 hours	10,000u load, then infusion to keep activated partial thromboplastin time 2 to 3 times normal	17-48 hours	0	9	0	0	
Dickie et al (1974)	4	12-16 hours	10,000u load, then 4-hourly by IV injection to keep Lee-White clotting time 2.5 times normal	72 hours	0	4	0	0	
TOTAL	32				0	30	1	0	1

[1] Duration of therapy until second pulmonary angiogram.

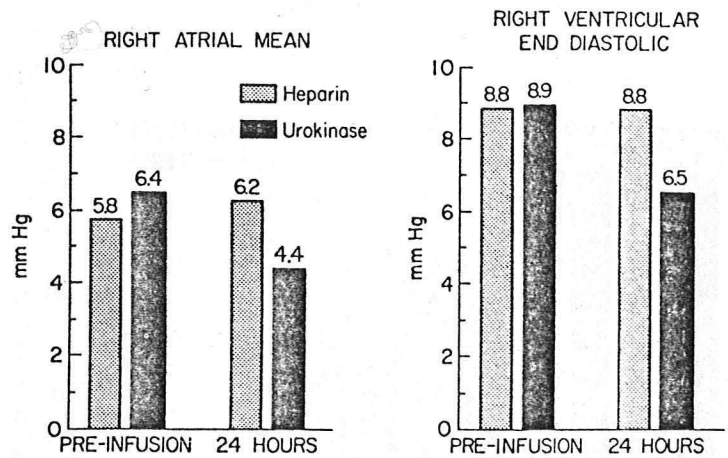
Abbreviations: NS = Not Stated.

b. Controlled clinical trials

The results of the national cooperative study, the Urokinase Pulmonary Embolism Trial were published in 1973. In the first 24 hours, urokinase gave significantly more lysis of pulmonary emboli than did heparin as estimated by hemodynamic measurements, lung scans and pulmonary angiography.

Hemodynamically, urokinase gave significantly greater improvement in right atrial mean pressure, right ventricular end diastolic pressure, (Figure 3), right ventricular systolic pressure, pulmonary artery mean pressure (Figure 4) and total pulmonary resistance than did heparin. There was no significant difference in the effect of the two drugs on A-VO_2 difference or cardiac index.

Lung scan perfusion defects prior to treatment with heparin were estimated as 25% and in urokinase as 27% of the total pulmonary vascular bed. Mean absolute improvement and lung scan perfusion defect was significantly greater at 24 hours with urokinase than with heparin, but by day 3 there was no significant difference in the rate of lysis between the two drugs. (Figure 5).

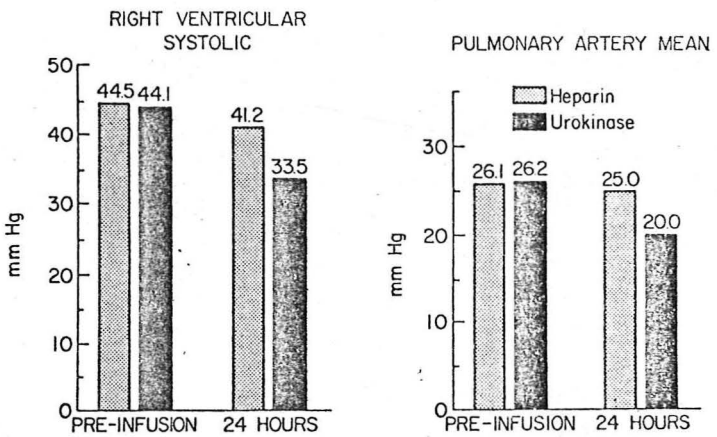


Urokinase - Heparin		
*Difference in mean change	-2.38 mm Hg	-2.63 mm Hg
Standard error	0.47	0.65
Critical ratio	5.1	4.1
RBO	0.000022	0.0018

* Adjusted difference

Figure 3

Mean preinfusion and 24-hour right atrial mean and right ventricular end-diastolic pressures.



	Urokinase–Heparin	
* Difference in mean change	−6.98 mm Hg	−4.28 mm Hg
Standard error	1.49	0.99
Critical ratio	4.7	4.3
RBO	0.00019	0.00065

*Adjusted difference

Figure 4

Mean preinfusion and 24-hour right ventricular systolic and pulmonary arterial mean pressures.

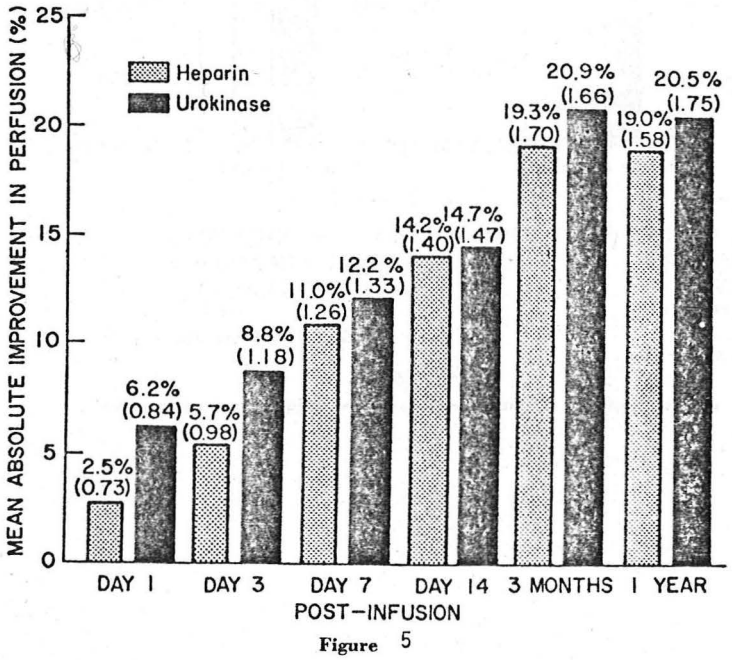


Figure 5

Mean postinfusion absolute improvement in lung scan perfusion defect. Mean preinfusion perfusion defect was 24.8% (SD 12.3) in heparin patients and 26.5% (SD 14.8) in urokinase patients. The standard error of the measurement is given in parentheses above each column with the mean absolute improvement in per-

Angiographically, both groups of patients showed on average moderately severe abnormalities in pulmonary angiograms. There was significantly greater improvement with urokinase than with heparin at 24 hours (Figure 6). Urokinase also gave significantly greater improvement in the pulmonary angiogram at 24 hours when the analysis was confined both to patients with massive embolism (Figure 7) and when confined to patients who were admitted with shock. (Figure 8). In this study, massive pulmonary embolism was defined as emboli involving at least 2 lobar vessels or its equivalent.

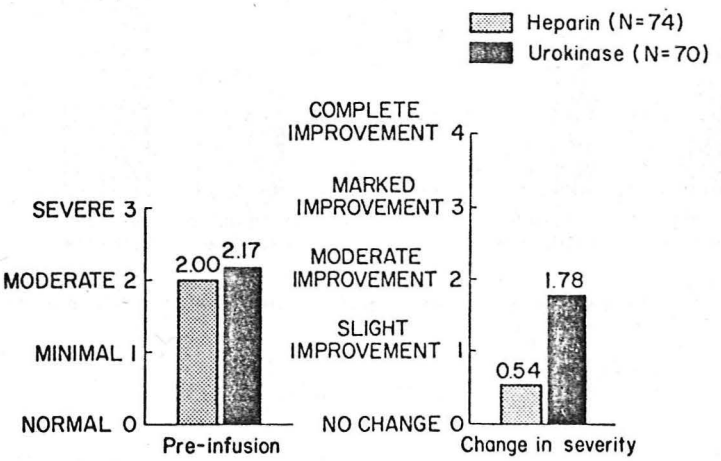


Figure 6

Mean preinfusion angiographic severity and mean change in severity at 24 hours.

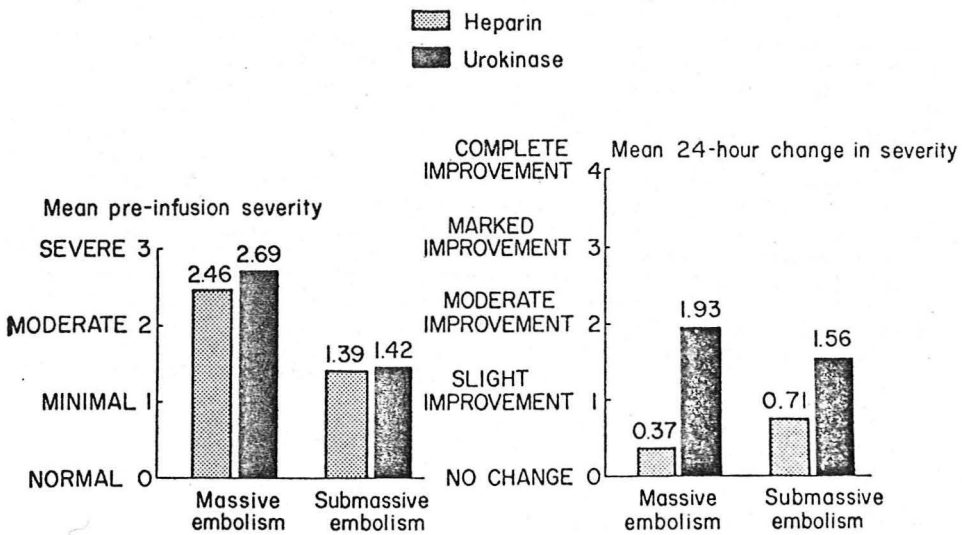


Figure 7

Mean angiographic preinfusion severity and change in severity by massiveness of embolism.

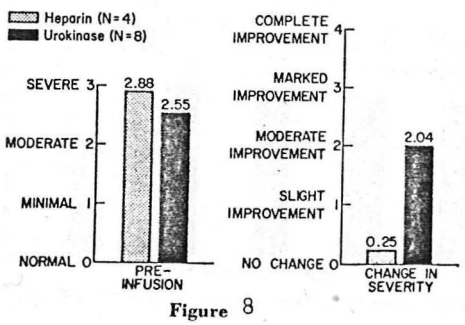
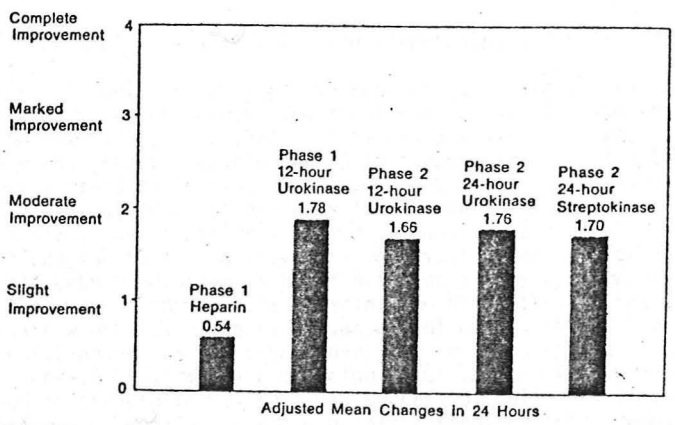


Figure 8

Mean angiographic preinfusion severity and change in severity for patients in shock (class II).

A second phase of the National Cooperative Study, the Urokinase-Streptokinase Embolism Trial (USET) was reported in the JAMA in 1974. The same data was published in several other places (Bell et al, 1974; Bell, 1975; and Bell, 1976). The study was designed to see if a more prolonged infusion of urokinase was of benefit and if streptokinase gave equal lysis. Consequently 167 patients with angiographically demonstrated pulmonary emboli were randomized to treatment with 12 hours of urokinase, 24 hours of urokinase or 24 hours of streptokinase. Evaluated angiographically, clot resolution with 12 hours of urokinase was similar to the phase 1 study and no different from a 24 hour infusion of urokinase or streptokinase.(Figure 9) When evaluated by lung scans, 24 hours of urokinase resulted in greater improvement than streptokinase therapy and this difference is significant in massive pulmonary embolism. Hemodynamically, the pulmonary artery pressures were lowered to a greater extent in the 2 urokinase treatment groups than the streptokinase group. However, the difference was not significant. The cardiac index showed a greater degree of improvement in patients treated with 24 hours of streptokinase but this difference was also not significant. Changes in the log of the total pulmonary resistances were nearly identical in three treatment groups.



Comparison of phase 1 and 2 results with angiographic 24-hour change as an endpoint.

FIGURE 9

The UPET and USET were not designed to demonstrate, nor did they demonstrate, any difference in mortality. Table 10 summarizes the results of both the phase 1 study and the phase II study with regard to major bleeding complications and death. Mortality rate was 7-9% which is similar to the experience in most other studies (Dalen and Alpert, 1975). In the UPET (Phase I) study pulmonary embolism caused or contributed to 4 of the 7 deaths in the heparin group. Major hemorrhage caused or contributed to 3 of the 6 deaths in the urokinase group.

TABLE 10

COMPLICATIONS OF THROMBOLYTIC THERAPY
FOR PULMONARY EMBOLISM
IN CONTROLLED CLINICAL TRIALS

PHASE	DRUG	N	MAJOR BLEED	DEATH WITHIN 2 WEEKS
I	HEPARIN	78	11 (14%)	7 (9%)
I	UROKINASE	82	22 (27%)	6 (7%)
II	UROKINASE (24 HR)	59	10 (17%)	4 (7%)
II	UROKINASE (24 HR)	54	7 (13%)	5 (9%)
II	STREPTOKINASE (24 HR)	54	10 (19%)	5 (9%)

c. Thrombolytic therapy in life-threatening pulmonary embolism.

There is only one prospective randomized clinical trial comparing streptokinase and heparin in the treatment of life threatening pulmonary embolism (Tibbutt et al, 1974). This was a small study with 17 patients randomly assigned to heparin and 13 to streptokinase. Streptokinase was given as a standard loading dose of 600,000 units, followed by an hourly infusion of 100,000 units per hour for 72 hours when pulmonary angiography was repeated. Seven patients failed to complete the trial because of deterioration and the fact that they remained hypotensive. Unfortunately, 5 of these had been randomized to heparin and only 2 received streptokinase. Of those that were randomized to heparin, one died after 18 hours and necropsy showed a new embolus. Two had a successful embolectomy. Two were changed to streptokinase; one improved moderately in 72 hours and one worsened and had a successful pulmonary embolectomy. Of the two that were randomly assigned to streptokinase, both had successful pulmonary embolectomies. The patients who were able to complete this controlled trial comparing streptokinase and heparin showed significantly greater lysis (by angiographic evaluation) with streptokinase. The patients on streptokinase also had significantly greater improvement in their pulmonary artery systolic pressures and mean pressures. (Figure 10).

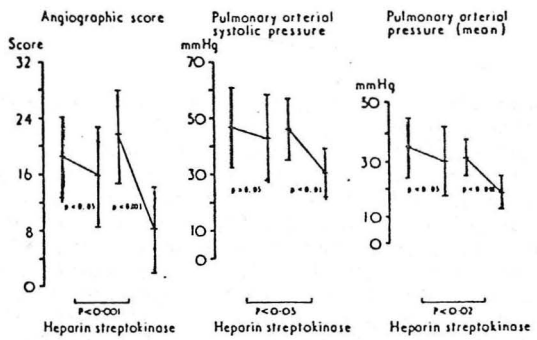


FIG. 10—Mean values (±1 S.D.) before and after 72 hours' treatment in respect of angiographic score, systolic, and mean pulmonary arterial pressures.

The patients in this study had their initial pulmonary angiograms scored by a system taking into account segmental filling defects and also absence of capillary perfusion in various regions. A maximum possible abnormality would be a score of 34. Figure 11. If patients had an angiographic score of 24 or more and a systolic blood pressure of 100 mm Hg or less there was a 70% chance of death or need for embolectomy. 7 patients met these criteria and unfortunately 6 were randomly assigned to heparin. However, this should be useful information for the design of any future evaluation of thrombolytic agents in life-threatening pulmonary embolism.

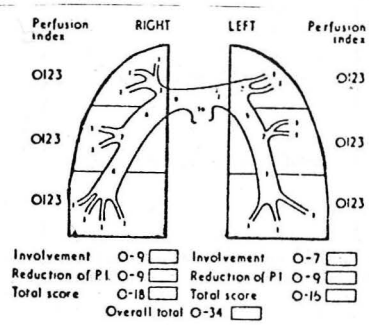


FIG. 11—Angiographic score chart: the right and left pulmonary arteries were regarded as having nine and seven major segmental branches respectively. Presence of a filling defect in any one of these branches scored one point. Presence of a filling defect proximal to segmental branches scored a value equal to number of segmental branches arising distally. Effect of embolism on opacification of peripheral vessels by contrast medium ("perfusion" index, P.I.) was scored for each of six lung zones: absent (3 points), severely reduced (2), mildly reduced (1), or normal (zero).

H. COMPLICATIONS

1. Bleeding

The hemorrhagic complication rate in the phase 1 study was very high with both urokinase and heparin (Table 11). Overt bleeding with a hematocrit drop of 5 to 10 points or requiring 2 units or less of transfusion was considered moderate; overt bleeding with a hematocrit drop greater than 10 points or requiring greater than 2 units of blood transfusion was considered severe. If both moderate and severe bleeding are considered significant then 21 (27%) of the patients with heparin bled and 37 (45%) of the patients with urokinase bled. This did not include 20 patients with unexplained drops in hematocrit of more than 5 points in each group. The cutdown site for the pulmonary angiogram required in the study was the site for bleeding in about 2/3 of the patients treated with urokinase and about 1/3 of the patients treated with heparin.

Table 11 Hemorrhagic complications[1]) by type and time of occurrence.

		Urokinase	Heparin
	Overt bleeding		
Early severe		14	5
Early moderate		15	4
Late severe		8	6
Late moderate		0	6
Total		37	21
	(Location of bleeding) cutdown bleeding		
Severe		8	4
Moderate		13	2
Total		21	6
	Spontaneous bleeding		
Severe		14	8
Moderate		2	7
Total		16	15
	Unexplained hematocrit falls		
Severe		5	1
Moderate		15	19
Total		20	20

[1]) Sites of spontaneous bleedings were similar in both groups. Most common sites were gastrointestinal (12 patients), retroperitoneal (6 patients) and intramuscular (4 patients).

In UPET heparin was initiated by a continuous infusion of 10 units per pound per hour. In an average sized person this dosage regimen delivers about 36,000 units of heparin per day. Two studies (Salzman et al, 1975 and Glazier et al 1976) have found significantly lower major bleeding with continuous intravenous heparin than with intermittent intravenous heparin. (Table 12).

TABLE 12

MAJOR BLEEDING DURING INTRAVENOUS HEPARIN THERAPY

AUTHOR	NUMBER OF PATIENTS	MAJOR BLEEDS (%)	AVERAGE 24 HOUR DOSE
	INTERMITTENT		
Saltzman 1975	72	6 (8%)	31,740
Glazier 1976	21	7 (33%)	32,808
Bynum 1977	62	8 (13%)	37,593
Mant 1977	36	4 (11%)	28, 861
	CONTINUOUS		
Saltzman 1975	69	1 (1%)	24,480
Glazier 1976	20	0 (0%)	25,488
Bynum 1977	52	3 (6%)	26,032
Mant 1977	46	6 (15%)	33,074

However, both of these studies used lower 24 hour doses of heparin near 25,000 units per day. A subsequent study (Mant et al 1977) found just as much major bleeding with continuous as with intermittent intravenous heparin. These investigators used a 24 hour dose of near 33,000 units for continuous heparin. In our own study just recently completed (Bynum et al 1977) we found no significant differences in major bleeding between continuous and intermittent intravenous heparin when all patients are considered. We anticipated that patients with certain risk factors (Table 13) might have an increased bleeding tendency and randomized these patients separately.

TABLE 13

RISK FACTORS FOR BLEEDING COMPLICATIONS

AGE GREATER THAN 60 YEARS
UREMIA
SEVERE HYPERTENSION
RECENT SURGERY OR TRAUMA
RECENT GASTROINTESTINAL BLEEDING
ANY DOCUMENTED HEMOSTATIC DEFECT
MASSIVE PULMONARY EMBOLISM

When our high risk patients are analyzed separately (Table 14), the patients who received intermittent intravenous heparin had significantly more major bleeding (29%) than those who received continuous (5%). However, in patients at low risk for bleeding intermittent intravenous heparin

in conventional doses of 100 units per Kg every 4 hours had no major bleeding. Interestingly the intermittent heparin was associated with a significantly lower incidence of recurrence in both low and high risk patients.

TABLE 14.

OUTCOME OF THERAPY IN HIGH AND LOW RISK PATIENTS

	INTERMITTENT	CONTINUOUS	P
HIGH RISK PATIENTS			
TOTAL	28	21	
MAJOR BLEEDING	8 (29%)	1 (5%)	<.05
RECURRENT THROMBO-EMBOLISM	2 (7%)	8 (38%)	<.025
LOW RISK PATIENTS			
TOTAL	31	27	
MAJOR BLEEDING	0 (0%)	2 (7%)	N.S.
RECURRENT THROMBO-EMBOLISM	1 (3%)	6 (22%)	<.05

In our study patients receiving intermittent heparin received significantly more (37,462 ± 1420 units/day) daily heparin than those receiving continuous heparin (25,892 ± 932 units/day) ($P < .001$). With intermittent intravenous heparin the patients with major bleeding had significantly higher Lee White clotting times and mean daily doses of heparin than patients who did not bleed (Table 15).

TABLE 15. INTERMITTENT INTRAVENOUS HEPARIN

	N	LWCT(min) Mean ± SD	DAILY HEPARIN (units/24 hr) Mean ± SD
NO BLEED	44	28.8 ± 15	39,619 ± 11,871
MAJOR BLEED	8	36.0 ± 20	44,217 ± 15,054
P		< .025	< .05

With continuous intravenous heparin the patients with recurrence had no lower Lee White clotting times or mean daily doses of heparin than patients without recurrence. (Table 16).

TABLE 16. CONTINUOUS INTRAVENOUS HEPARIN

	N	LWCT(Min) Mean ± SD	DAILY HEPARIN (Units/24 hr) Mean ± SD
NO RECURRENCE	35	31.7 ± 14	25,515 ± 5,351
RECURRENCE	17	29.5 ± 12	26,934 ± 9245
P		N.S.	N.S.

The questions that are unanswered are: 1) Will a lower dose of intermittent heparin (such as 60 units/Kg IV every 4 hours) maintain the benefit of lower recurrence rate without the problem of increased major bleeding in high risk patients? 2) Will more careful adjustment of the dose of continuous intravenous heparin reduce the recurrence rate without more major bleeding?

We have a phase II clinical study designed to answer these questions.

a. Mechanism of coagulation defect during thrombolytic therapy.

The mechanisms of the coagulation defects associated with fibrinolysis have been reviewed by Kowalski (1968). The major mechanisms are: 1) Inhibition of fibrinogen-fibrin conversion by early FDP, especially fragment Y. The early FDP inhibit thrombin release of fibrinopeptides from fibrinogen. 2) Effect on platelets: Platelet adhesiveness is inhibited by early FDP or complexes of fibrin monomer with early FDP. Complexes of fibrin monomer with fibrinogen have an opposite effect and enhance platelet aggregation. 3) Defective structure of fibrin results when FDP are incorporated within the clot (Alkjaersiz et al 1959).

b. Treatment of severe bleeding during thrombolytic therapy.

Fatal hemorrhage has occurred in only 0.6% of patients treated with streptokinase for deep venous thrombosis (Brogden et al, 1973). If a patient undergoing thrombolytic therapy develops life threatening hemorrhage which does not respond to stopping the lytic infusion and to blood transfusions, epsilon aminocaproic acid (EACA) should be used. (McNeal and Douglas, 1976). The recommended dose is 5 g intravenously slowly followed by 1.25 g per hour until bleeding is under control. No more than 30 g should be given in 24 hours and rapid intravenous infusion should be avoided to prevent hypotension, bradycardia and arrhythmias (Levine, 1975). After the EACA infusion is stopped there is a potential danger of rebound bleeding. EACA potentiates rather than inhibits fibrinolysis due to urokinase at blood levels of EACA between 10^{-2} and 10^{-3} M. These intermediate concentrations of EACA are present as the blood levels fall. Lower levels again inhibit fibrinolysis due to urokinase. (Thorsen et al 1974b).

EACA acts as a plasminogen activator inhibitor in concentrations as low as 10-4 and a plasmin inhibitor in higher concentrations above 5 X 10^{-2}M. EACA also acts partly by interacting with fibrin and rendering it resistant to proteolysis (Ambrus et al 1970).

2. Recurrence

In the UPET there was a definite or probable recurrence of pulmonary embolus in 14 (17%) of patients treated with urokinase and 18 (23%) of the patients treated with heparin.

Table 17 Morbidity and mortality within the two-week follow-up period.

Recurrent pulmonary embolism	Urokinase	Heparin
Definite	5	7
Probable	9	11
Inferior vena cava plication	3	9
Pulmonary embolectomy	0	0
Acute myocardial infarction	0	1
Death within 2 weeks	6	7

	1-S	1-M	2-S	2-M
2 week case fatality rate[1]) by patient class	$\frac{4}{68} = 5.9\%$	$\frac{4}{78} = 5.1\%$	$\frac{3}{3} = 100\%$	$\frac{2}{11} = 18.2\%$

[1]) Causes of death were similar in both groups. Patient class subgroups are:
1-S: Submassive embolism not in shock
1-M: Massive embolism not in shock
2-S: Submassive embolism in shock
2-M: Massive embolism in shock

When streptokinase is used plasma plasminogen levels are reduced lower than with urokinase (Bell, 1975) and re-thrombosis could produce thrombi more resistant to lysis because of less plasminogen incorporated within the clot. In an uncontrolled study of treatment of ileofemoral thrombosis with streptokinase the poor results were associated with a lower plasminogen level and a slowly rising fibrinogen level during therapy. (Dhall et al 1978). The possibility of improving results by treatment with ancrod which keeps fibrinogen levels low was proposed. A study comparing the sequence of streptokinase, ancrod, oral anticoagulants with the sequence streptokinase, oral anticoagulants in deep venous thrombosis showed excellent results with both approaches (Tibbutt et al, 1977). Virtually all authorities recommend following thrombolytic therapy with anticoagulants because of bad experience with re-thrombosis in some of the early pilot studies.

I. NEW APPROACHES

1. The combination of intravenous heparin therapy and low doses or brief courses of streptokinase were evaluated in dogs with experimental pulmonary emboli and were shown to be syngergistic, producing as much resolution as did standard high doses of streptokinase alone (Cade et al, 1974). The same group evaluated intravenous heparin and low dose streptokinase therapy in 13 patients with major pulmonary embolism and 32 patients with deep venous thrombosis of the lower extremities. The results were comparable to high dose streptokinase results in the patients with pulmonary emboli and gave a degree of resolution between the results of streptokinase and heparin for deep venous thrombosis. Unfortunately major bleeding occurred in 2 of the 13 patients with pulmonary embolism and 2 of the 32 patients with deep venous thrombosis. Also, because of the danger of inducing a sustained hyperplasminemia with very low doses of streptokinase, frequent laboratory testing and modification of the dose was necessary. The regimen appears to be more trouble than high dose streptokinase therapy and did not avoid major bleeding.

2. Intermittent Streptokinase + Plasminogen

Theoretically part of the reason for failure of lysis during conventional streptokinase therapy is due to the marked reduction of plasminogen in plasma. With lower plasminogen levels less would be available to attach to fibrin or to be activated by plasminogen activator absorbed to the clot. To avoid low plasminogen levels, 12 patients with deep venous thrombosis were treated with single daily infusions of 600,000 units of streptokinase and 90 mgs of plasminogen daily for 5 days (Kakkar et al, 1975; Scully et al, 1977). The results were excellent with complete lysis in 8 patients and good lysis in 4. Five consecutive patients treated with the same dose of streptokinase alone showed no lysis. The commercially available plasminogen that was used in this study is partially degraded and has lysine as the N-terminal amino acid. The partially degraded form of plasminogen having lysine rather than glutamic acid as the N-terminal amino acid has been shown to have greater affinity for fibrin (Thorsen 1975). This method appears promising and worthy of further investigation.

3. Sequential use of Streptokinase and Ancrod

The sequential use of streptokinase and ancrod followed by oral anticoagulation was no better than streptokinase followed by oral anticoagulation in the treatment of deep venous thrombosis of the lower extremity (Tibbutt et al, 1977).

4. Intermittent Bolus High Dose Streptokinase

An intermittent dosage scheme of streptokinase 600,000 units as a loading dose over 30 minutes and repeated injections of 250,000 units at 24 hour intervals cause plasminogen to fall to 17% of its pre-treatment value and then rise about 50% of its initial value. No bleeding was observed but 3 patients with deep venous thrombosis evaluated were not benefited. (Verstraete, 1978).

J. SUMMARY

Thrombolytic agents can cause dramatically more lysis of pulmonary emboli and deep venous thrombi than treatment with heparin alone. At times the lysis is poor. There is no completely reliable way of predicting poor lysis, but age of the thrombus or embolus and extent of complete obstruction are probably the most important factors. There is a high incidence of major bleeding complications with thrombolytic agents. The risk of major bleeding outweighs minor benefits of treating small to moderate size pulmonary emboli or deep venous thrombosis confined to the calf.

In all thrombolytic therapy patients at high risk for bleeding should be avoided and invasive procedures should be kept to a minimum to avoid major bleeding.

The most clear cut indication for thrombolytic agents is major deep venous thrombosis that is extensive and has extended above the knee. Thrombolytic agents very frequently cause complete lysis and preservation of venous valves. This will likely avoid severe post thrombo phlebitic symptoms.

The indications for thrombolytic therapy in major and massive pulmonary embolism are less clear cut. When pulmonary angiography shows massive pulmonary emboli with poor capillary filling phase of over 70% of the pulmonary vascular bed, thrombolytic agents may not cause lysis rapidly enough to salvage the patient. If the patient remains hypotensive with poor organ function, pulmonary embolectomy may still be needed. In the patient with major pulmonary embolism slightly less extensive, thrombolytic agents quickly lyse the majority of the emboli; a margin of reserve lung function is obtained that benefits the patients if emboli recur within the first few days.

Thrombolytic therapy is a major advance in the treatment of extensive deep venous thrombosis. Its benefit in major pulmonary embolism in terms of end functional status or survival has not been proven.

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