Consensus Development

Thrombolytic therapy in treatment

SUMMARY OF AN NIH CONSENSUS CONFERENCE

A National Institutes of Health consensus development conference, held at NIH on 10-12 April 1980, addressed the issue of thrombolytic therapy for the management of acute deep-vein thrombosis and pulmonary embolism. The thrombolytic agents considered were urokinase and streptokinase. At NIH, consensus development conferences bring together biomedical research scientists, practising physicians, consumers, and others as appropriate in an effort to reach general agreement on the safety and effectiveness of a medical technology. That technology may be a drug, device, or medical or surgical procedure.

A consensus development panel, after listening to expert presentations at the conference, issued the following consensus statement.

For over three decades, the primary method of therapy used by almost all physicians for the management of acute deep-vein thrombosis and pulmonary embolism has been anticoagulation. This form of therapy has become so ingrained in medical practice that physicians, while still concerned over the bleeding risk associated with the use of anticoagulants, nevertheless seem secure in the belief that they are providing optimal, if not ideal, therapy for these disorders. With the advent of thrombolytic therapy, this is no longer true for a large number of cases. Anticoagulation for the management of acute deep-vein thrombosis and pulmonary embolism, while usually effective in preventing or slowing further thrombus formation in veins and significantly diminishing the likelihood of subsequent or recurrent embolisation, does *not*:

- eliminate the source of subsequent embolisation in the deep veins during the acute attack;
- alleviate the haemodynamic disturbances associated with the thrombosis or embolism;
- prevent subsequent valvular damage to the deep veins and the development of persistent venous hypertension and associated symptoms in the lower extremities which may predispose to recurrent deep-vein thrombosis and pulmonary embolism;
- prevent permanent impairment to the pulmonary vascular bed and, in patients with more extensive involvement, persistence of pulmonary hypertension.

The reason that patients with acute deep-vein thrombosis and pulmonary embolism treated with anticoagulation alone are subject to these complications is that such therapy has no acute effect on previously formed thrombi or emboli. Its role is primarily that of secondary intervention—that is, prophylaxis against further thrombus growth, recurrence, and embolisation. The natural history of underlying thrombi and emboli treated with anticoagulation alone is mainly one of organisation and recanalisation.

Uses of thrombolytic treatment

From these considerations it is apparent that ideal therapy for acute deep-vein thrombosis and pulmonary embolism requires either the surgical removal or lysis of the thrombus or embolus so as to restore to normal the haemodynamics and integrity of the vasculature and the subsequent prevention of recurrence of thrombosis. On the basis of present experience a surgical approach is usually unsuccessful except under very limited conditions.

However, the lysis of thrombi and emboli can be successfully accomplished in a large number of patients through the proper use of thrombolytic agents. When used in conjunction with anticoagulants thrombolytic therapy can achieve the objectives of ideal management as follows:

- lyse thrombi and emboli and restore the circulation to normal;
- normalise the haemodynamic disturbances and reduce morbidity;
- prevent venous valvular damage and subsequent venous hypertension in the lower extremities; and
- prevent permanent damage to the pulmonary vascular bed and reduce the likelihood of persisting pulmonary hypertension.

While there are compelling reasons to use this new form of therapy in the management of acute deep-vein thrombosis and pulmonary embolism, it must be recognised that there are risks associated with the use of thrombolytic therapy. Therefore, the administration of thrombolytic agents should be encouraged only in those situations where the benefits to be achieved outweigh the hazards. At present this would be for those patients who are suffering from proximal deep-vein thrombosis—that is, thrombosis affecting the popliteal vein or the deep veins of the thigh and pelvis—and for those with pulmonary emboli with significant haemodynamic disturbances or where there has been obstruction of blood flow to a lobe or multiple segments, providing:

- the diagnosis is established;

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Members of the consensus development panel were Dr Sol Sherry, Temple University School of Medicine, Philadelphia, (chairman); Dr William R Bell, the Johns Hopkins University School of Medicine, Baltimore; Dr F H Duckert, Katonsspital, Basel, Switzerland; Dr Anthony P Fletcher, Washington University School of Medicine, St Louis; Dr Victor Gurewich, St Elizabeth's Hospital, Boston; Dr David M Long, La Mesa, California; Dr Victor J Marder, the University of Rochester, Rochester, New York; Dr Harold Roberts, University of North Carolina, Chapel Hill, North Carolina; Dr Edwin W Salzman, Beth Israel Hospital, Boston; Dr Arthur Sasahara, Veterans Administration Hospital, West Roxbury, Massachusetts; Dr Marc Verstraete, University of Leuven, Leuven, Belgium.

● the severity of the clinical problem exceeds the risk of bleeding associated with a major contraindication;

● proper care is taken in the handling of the patient and in avoiding all but absolutely essential invasive procedures; and

● there is a clear understanding of the details of therapy, including monitoring, management of bleeding complications, and the control of subsequent anticoagulation.

When properly used, in tandem with anticoagulation, thrombolytic therapy as currently practised represents a significant advance in the management of proximal acute deep-vein thrombosis and the more severe forms of pulmonary embolism. With further developments aimed at improving its efficacy and reducing the bleeding risk, this form of therapy could become the initial treatment for all forms of acute deep-vein thrombosis and pulmonary embolism.

This consensus statement was arrived at following discussion of a series of questions.

(1) Are there proved benefits for the use of thrombolytic therapy in currently approved indications—that is, the more severe forms of acute deep-vein thrombosis and pulmonary embolism?

There are proved benefits as follows.

● Thrombolytic therapy lyses thrombi in the deep venous system and emboli in the pulmonary circulation, and the thrombi and emboli disappear more rapidly than with heparin therapy. These observations are based upon a number of controlled clinical trials in which treatment efficacy was assessed by objective means such as serial pulmonary angiography, perfusion lung scanning, and contrast venography.

● Thrombolytic therapy results in a greater improvement or normalisation of the abnormal haemodynamic responses to pulmonary embolisation than is observed with heparin therapy. These observations are based on serial studies of selected haemodynamic measurements from the right heart and pulmonary circulation. It has also been shown that lessening of pulmonary hypertension may be observed as early as one and a half hours following initiation of thrombolytic therapy, reaching a maximum in approximately six hours.

● Thrombolytic therapy helps to prevent venous valvular damage and subsequent venous hypertension in the extremities by rapid and more complete lysis of thrombi. It has been demonstrated that patients treated with thrombolytic therapy have a much higher frequency of maintenance of intact and functioning venous valves than do patients treated with heparin alone.

● Thrombolytic therapy may prevent permanent damage to the pulmonary vascular bed by lysing emboli and restoring the pulmonary circulation to normal. In contrast, it has been observed that residual emboli usually persist in patients treated with heparin alone. The presence of such residual emboli, especially significant in those suffering pulmonary embolism, may result in persistent pulmonary hypertension.

(2) What are the risks associated with the use of thrombolytic agents?

Review of the literature indicates that of the undesirable effects associated with current thrombolytic therapy, bleeding poses the major potential risk.

The bleeding associated with thrombolytic therapy is more frequent than with conventional anticoagulants, but this is primarily related to bleeding from sites of invasive procedures. The type of bleeding observed in association with thrombolytic agents can be placed into two broad categories:

● Superficial or surface bleeding, observed mainly at invaded or disturbed sites—for example, venous cut-downs, arterial punctures, sites of recent surgical intervention, etc. This type of bleeding is inherent in the nature of thrombolytic therapy since the use of thrombolytic agents is predicated on their ability to lyse fibrin. One can minimise bleeding at these sites by appropriate patient management and avoidance of procedures that disturb the integrity of the vascular system.

● Internal bleeding observed in the gastrointestinal tract, genitourinary tract, vagina, intramuscular, retroperitoneal, intracerebral, etc. Although this type of bleeding occasionally happens during thrombolytic therapy with a recognisable incidence, it is not statistically different from the incidence of bleeding seen with conventional anticoagulants. However, there is an incidence of cerebral haemorrhage of about 1% associated with thrombolytic therapy compared with a 0·5% incidence observed with heparin.

With the use of good clinical judgment many of these bleeding problems can be avoided by appropriate case selection and management.

Additional undersirable effects that have been observed in association with thrombolytic therapy include fever and allergic reactions. These occur at a low frequency, are mild, and seldom result in any physiological injury or the need to discontinue therapy. Anaphylactoid reactions observed with older preparations no longer in use are very rarely observed with the presently employed agents. When such reactions have been observed they uniformly respond to conventional therapy.

(3) What are the guidelines for patient selection?

Selection of patients for thrombolytic therapy should be based on the following considerations:

● The presence of an appropriate clinical indication including a documented diagnosis and evidence that the thrombus is of recent origin ($\leqslant$ 7 days).

● Careful evaluation of contraindications, which include the following.

Absolute—(*a*) active internal bleeding. (*b*) recent (within two months) cerebrovascular accident or other active intracranial process. There is evidence that currently used thrombolytic regimens carry the hazard of inducing cerebral haemorrhage in those with a recent history of stroke. (However, studies are currently under way using lower agent dosage for the treatment of stroke.)

Relative—Major: (*a*) recent ($<$ 10 days) major surgery, obstetric delivery, organ biopsy, previous puncture of non-compressible vessels; (*b*) recent serious gastrointestinal bleeding; (*c*) recent serious trauma; (*d*) severe arterial hypertension ($\geqslant$ 200 mm Hg systolic or $\geqslant$ 110 mm Hg diastolic). Minor: (*a*) recent minor trauma including cardiopulmonary resuscitation; (*b*) high likelihood of a left heart thrombus—for example, mitral disease with atrial fibrillation; (*c*) bacterial endocarditis; (*d*) haemostatic defects including those associated with severe hepatic or renal disease; (*e*) pregnancy; (*f*) age $>$ 75 years; (*g*) diabetic haemorrhagic retinopathy.

(4) Assuming there are proved benefits and a favourable risk : benefit ratio, why are these drugs not being used more frequently?

The panel agreed that while some rationales for deciding against the use of thrombolytic agents were reasonable, such as an inadequate clinical indication or the risk of serious haemorrhage, others were unreasonable. These unreasonable rationales are partly the result of reports of the large multi-centre urokinase and streptokinase pulmonary embolism trials with their complex biochemical and physiological studies that required many invasive procedures, and also of the early experience using thrombolytic agents that were less pure than current products and which caused more frequent pyrogenic and allergenic side effects. The unreasonable rationales include the following:

Fear of bleeding—The urokinase and streptokinase pulmonary embolism trials showed a high incidence of bleeding both with thrombolytic agents and with heparin. However, the incidence of significant bleeding was only 9% for urokinase-streptokinase and 4% for heparin. The incidence of major bleeding complications with lytic agents during recent clinical experience—that is, since the drugs have been available for general use by doctors—has been about 5%. This is based on the patient treatment forms returned to pharmaceutical manufacturers during the continuing surveillance period requested by the Bureau of Biologics, Food and Drug Administration.

Need for additional invasive procedures—The diagnostic procedures

required for thrombolytic therapy are no different from those required for heparin. Objective diagnostic procedures are required for both.

Confusion regarding dose regulation—There are many directives suggested by the package insert and the general literature that are complex and confusing. For instance, increasing the dose of streptokinase in order to decrease the proteolytic effect is scientifically accurate but is unnecessary with a fixed-dose schedule. Additionally, the streptokinase resistance test is unnecessary, given the 90% expectation of inducing a lytic state by the standard loading dose followed by a fixed dose schedule. Altering or eliminating such directives in the package insert would simplify treatment.

Limited availability of laboratory assays—Although research studies used many highly sophisticated assays for following thrombolytic treatment, any one of a number of assays can now be used to reflect the circulating "lytic state," the simplest of which is the thrombin time. Whatever the choice of the physician (plasminogen, lysis time, prothrombin time, activated partial thromboplastin time, fibrin-fibrinogen degradation products, fibrinogen, etc) at least one of these assays will be available for use by the practitioner in any hospital laboratory.

"*Evaluate response to heparin first*"—Any delay in instituting lytic therapy in order to determine whether heparin achieves an initial good response will decrease the potential for optimal response. Therefore, therapy with urokinase or streptokinase should not be deferred after the diagnosis has been established for any reason other than the presence of a serious contraindication to use.

Decision by committee—The decision to treat need not be made by a committee; such a decision may be made by an informed clinician who is prepared to manage such a patient with a lytic agent.

(5) What are the guidelines for patient management and monitoring?

● The diagnosis should be established with objective techniques. If pulmonary angiography is performed the upper extremity should be used.

● Before thrombolytic infusion, the following laboratory tests are indicated: a thrombin time (TT), activated partial thromboplastin time (APTT), prothrombin time (PT), packed cell volume, and platelet count. If heparin has been given it should be discontinued and the TT or APTT should be less than twice the normal control value before thrombolytic therapy is started.

● Begin the thrombolytic infusion. During therapy no invasive procedures should be performed with the exception of careful venepuncture with a 22- or 23-guage needle for therapeutic monitoring. If essential, arterial blood gas studies can be performed (in the arm), but digital compression of the puncture site for at least 30 minutes is mandatory. The patient should be at strict bed rest and pressure dressings applied to previously invaded sites. No new medication should be added to the therapeutic regimen unless absolutely essential. No medication should be added to the bottle containing the thrombolytic agent.

● Vital signs—pulse, temperature, respiratory rate, and blood pressure—should be measured every four hours during infusion. To avoid dislodgment of deep-vein thrombi the blood pressure should not be measured in the legs.

● Therapeutic monitoring should be performed by using the thrombin time or activated partial thromboplastin time (if neither is available the prothrombin time can be employed). This should be performed three to four hours after institution of the thrombolytic agent (to identify and confirm activation of the fibrinolytic system). Opinions differ regarding the frequency of additional monitoring and its usefulness in predicting or controlling clinical efficacy and bleeding complications. When the TT or APTT is measured simultaneous measurement of packed cell volume is recommended.

● Should uncontrollable bleeding commence, the thrombolytic infusion should be discontinued and, if necessary, blood loss and reversal of the bleeding tendency can be effectively managed with whole blood (preferably fresh blood), packed red blood cells, and cryoprecipitate or frozen plasma.

● Following completion of the thrombolytic infusion, which will vary in duration according to the agent used and the type of the lesion being treated—for example, deep-vein thrombosis or pulmonary embolism (see package insert for details)—the patient should be placed on anticoagulants. After an interval of three to four hours following discontinuation of the thrombolytic agent, the TT or the APTT should be measured. When the results of this test no longer exceed twice the normal control value, heparin, without a loading dose, should be instituted and controlled according to standard procedures. This should then be followed by warfarin in the conventional manner.

(6) What are the economic aspects involved in thrombolytic therapy?

The thrombolytic agents available at present, streptokinase and urokinase, are expensive drugs, especially urokinase, and their use in patients with venous thrombosis or pulmonary embolism increases the cost of management of the acute thrombotic event. On the other hand, the economic burden imposed on society by the late morbidity of proximal venous thrombosis may be relieved by more widespread use of thrombolytic therapy, which under optimal circumstances restores venous patency and valvular function and prevents the subsequent development of the postphlebitic syndrome. Patients with phlebographic demonstration of complete lysis of proximal venous thrombi by thrombolytic treatment are spared the usual sequelae of venous stasis and their associated costs, which have been estimated at a total of nearly $40 000 per patient over a 10-year period in severe cases. The frequency of post-thrombotic sequelae in patients with thrombi in the popliteal, femoral, or iliac veins is sufficiently high to make thrombolytic therapy cost-effective in this group.

In pulmonary embolism, analysis of cost:benefit ratio is more difficult, for no monetary value has been assigned to the late benefits of improved pulmonary capillary flow and freedom from pulmonary hypertension that appear to follow the use of thrombolytic agents. Analysis of the economic aspects of this issue awaits further data.

(7) What should be the direction for future clinical research?

During the first day of the conference, the basic biochemistry of the fibrinolytic system as it relates to thrombolytic agents was reviewed. The highlights of this session included a discussion of the following: (*a*) specific activators of plasminogen, including high and low molecular weight urokinase; (*b*) the mechanism of action of streptokinase-plasminogen complex as a plasminogen activator; (*c*) the physiological activators of plasminogen; (*d*) natural inhibitors of plasmin and urokinase, including the kinetics of inhibition of plasmin by α_2 anti-plasmin; (*e*) the clinical manifestations of a patient with an abnormal plasminogen which resulted in a thrombotic tendency; (*f*) the use of synthetic substrates for assessment of various components of the fibrinolytic system; and (*g*) the detailed biochemical characterisation of glu and lys plasminogen. Mechanisms of in-vivo fibrinolysis were reviewed. In addition, a newly identified plasma protein (histidine-rich glycoprotein), which has the capacity to block the binding of plasminogen to fibrin, was reported. Preliminary data suggested that human tissue activator of plasminogen was a more selective activator of fibrinolysis than urokinase.

On the basis of the foregoing, the possible therapeutic role of new thrombolytic agents should be evaluated, such as streptokinase-plasminogen complex, activators of tissue origin, B chain-streptokinase complex, and the like.

There is also a need for further evaluation of current tests in terms of predicting thrombolytic success and bleeding. In addition, simple and practical tests reflecting or indicative of fibrin (thrombus) dissolution are highly desirable and would be a substantial contribution to further progress in this field.

Further clinical research is also required to evaluate the effects of different regimens involving dosage, durations, and combinations with other agents such as plasminogen and heparin. More information is needed on the efficacy and diminished risk of bleeding when streptokinase or urokinase is administered regionally rather than systemically. Investigations should also be encouraged for other indications of thrombolysis, including acute myocardial infarction.