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Anticoagulant and Antithrombotic Therapy in Deep Venous Thrombosis and Pulmonary Embolism

Paul D. Stein, MD*

Historical Perspective

The treatment of deep venous thrombosis and pulmonary embolism has been a long and continuing interest of physicians at Henry Ford Hospital. Heparin was discovered by Jay McLean in 1916 when he was a student in the laboratory of Dr. W.H. Howell at Johns Hopkins University (1,2). The anticoagulant was named heparin because it came from dog's liver (2). Results of investigations of this heparphosphatid were described by Howell and Holt in 1918 (3). The use of heparin as an anticoagulant for blood transfusion was explored at Henry Ford Hospital in 1924 (4), where the prevention of experimentally produced thrombosis and pulmonary embolism with heparin was studied (5). At that time, untoward reactions resulted from the injection of enough heparin to render even small amounts of blood incoagulable; therefore, full doses, as we use today, were not given. In 1928, however, heparin was purified sufficiently to initiate more extensive use in patients (6). The use of heparin in the management of thrombosis of veins following injury was reported in 1937 (7). By 1940, 440 patients had been given prophylactic heparin to prevent pulmonary embolism following various operative procedures (8). McClure and Lam (9) presented their early experience with the use of heparin for the treatment of pulmonary embolism or deep venous thrombosis in 11 patients. By 1941, systemic heparin had been administered to 30 patients at Henry Ford Hospital, and 24 of these patients were treated because of pulmonary embolism (10). The duration of treatment was unknown, and at that time two days of treatment was considered a reasonable period (9). In the early 1940s, oral anticoagulants with dicumarol became possible. By 1943, the experience with this drug, administered on an investigative basis only, included 637 patients throughout the world (11). Lam (11) reported results of treatment with dicumarol in 18 patients. Along with the vast experience obtained with anticoagulants in subsequent years, a huge amount of literature has been written on the use of anticoagulants in the prevention and treatment of deep venous thrombosis and pulmonary embolism. The following is an in-depth review of this subject in an attempt to crystallize the critical points related to the benefits and risks of anticoagulant therapy in these conditions.

The Problem of Deep Venous Thrombosis

The intensity of prophylactic drugs and procedures for the prevention of deep venous thrombosis can be tailored to the risk of its development with consideration of the hazards of bleeding complications. For this reason, some background regarding the occurrence of deep venous thrombosis is relevant. The aggregate incidence obtained from several studies of lower limb thrombosis in unselected autopsies is 43% (460 of 1,072 patients), and we observed leg vein thrombi in 48% of unselected patients at autopsy (12). Based upon review of numerous autopsy studies, the incidence of thrombi in the calves is higher than in the thighs, and thrombi in the thighs alone are the least common (12).

Numerous anatomic structures in the legs have been cited as sources of pressure causing decreased flow. Examples of such anatomic structures are the soleus muscle which compresses the posterior tibial vein, the adductor ring which compresses the popliteal vein, and the inguinal ligament which compresses the femoral vein. Since stasis is thought to be the single most important factor contributing to thrombosis, the high incidence of thrombi in these veins may at least in part be accounted for by these pressure points. Intramuscular veins are particularly dependent on muscular contractions for emptying because they are thin-walled and tortuous and have no venous impulse. With inactivity they become distended by a stagnant column of blood. The high incidence of thrombosis found in the intramuscular veins may be explained by these characteristics.

Valve pockets are frequent sites of thrombus origin. Five of the six patients in our study who had small (less than 0.5 cm) thrombi had them within valve pockets, and some of the larger thrombi could clearly be traced to origins in valve pockets (12). Clinical venography has demonstrated pooling of contrast medium at these sites. The eddying of blood with consequent sieling of platelets and leukocytes within these structures presumably creates a situation wherein thrombosis is precipitated. In every case in which the thigh and calf were thrombosed in continuity, the thrombi in the calf were older than those in the thigh (12). Histological investigations have shown no distinction between venous thrombosis in patients who had clinical evidence of inflammation (thrombophlebitis) and those who were asymptomatic (phlebothrombosis). The presence of a thrombus can induce inflammation in the underlying wall of the vein, which in some patients is extensive enough to produce pain, tenderness, swelling, and fever.

The autopsy incidence of deep venous thrombosis increases with age (13). The rate of occurrence was 17% among patients...
aged 30 to 39 years, 37% in patients aged 40 to 49, and 73% in octogenarians. Unfortunately, the risk of bleeding with heparin also increases with age, at least in females (14). Among females aged 60 or older, 50% had bleeding with heparin, as compared to younger females or males who had a 10% to 19% incidence of bleeding.

An impression of the incidence of venous thrombosis in various clinical circumstances can be obtained by noninvasive studies, particularly $^{125}$I-fibrinogen leg scans and impedance plethysmography (15).

The sensitivity and specificity of the diagnostic test must be considered in evaluating diagnostic data. Based upon pooled data reported from several investigators, each of which was cited by Gallus (15), 91% of patients with abnormal leg scans showed thrombi identified by venography. This may imply a lack of sensitivity of the venogram or a false-positive fibrinogen scan. Only 2% of patients with normal fibrinogen scans showed abnormal venograms. Thus, if the leg scan is abnormal, venous thrombosis is likely present.

The incidence of venous thrombosis, particularly of veins of the thigh, may be even higher than suggested by leg scans. Only 60% of patients with abnormal venograms had abnormal scans, and 22% of patients with normal venograms showed abnormal scans (15). Again, this may be interpreted either as false-positive scans or as scans having more sensitivity than the venograms. The latter is likely, particularly regarding thrombosis in the veins of the calves. The venogram, particularly of the calves, may not be sensitive. Among patients at autopsy in whom we performed postmortem venograms, in approximately 90% of the examinations of the veins in the thigh, the venographic impression corresponded to the anatomic findings (12). However, filling of the calf veins in general was less adequate. Apparent filling defects or absence of vessels were unreliable guides to the presence of thrombosis in the calf veins.

The impedance plethysmogram may relate closer to the venogram than the fibrinogen leg scan because both the impedance plethysmogram and venogram are more sensitive for the detection of thrombi of the veins of the thighs than of the calves. Among 169 abnormal venograms, the impedance plethysmogram was positive in 92% (16). Among 305 patients with normal venograms, the impedance plethysmogram was negative in 96% (16). Among patients with suspected pulmonary embolism and normal impedance plethysmograms, only 10% (two of 20) had pulmonary embolism by angiography (17), which suggests that the plethysmogram may have some value as a noninvasive screening test.

Calf vein thrombosis is less likely to lead to pulmonary embolism than thrombosis of the thigh veins. Among 21 patients with thrombosis of the calf veins, none showed an abnormal ventilation/perfusion scan, whereas if both the calf and thigh veins were involved, 53% (eight of 15) showed abnormal ventilation/perfusion scans (18).

**Who is at Risk of Deep Venous Thrombosis?**

Patients undergoing orthopedic surgery or suffering from femoral fractures are commonly recognized to have a high risk of deep venous thrombosis. The extent of risk, however, is striking. Among 65 patients with femoral fractures, 43% had deep venous thrombosis, and pooled data following orthopedic surgery, which included over 1,000 patients among references cited by Sasahara et al (17), showed a 47% incidence of deep venous thrombosis. Perhaps even more striking, although based upon only 63 patients, was a 51% incidence of deep venous thrombosis following thoracic surgery (19). Major surgery is associated with a 25% incidence of deep venous thrombosis (20). Acute myocardial infarction, when studied by sensitive methods (fibrinogen leg scan), carries about the same risk (24%) (17). Childbirth seems to carry a relatively small risk (3%) of deep venous thrombosis (15).

In evaluating these data it is important to recognize that fibrinogen scans and impedance plethysmography are sensitive tests, and the incidence of venous thrombosis may be considerably higher than it would seem based on clinical evaluation. Signs and symptoms of venous thrombosis occur in only 50% of patients in whom the fibrinogen scan shows thrombi (21). Also, only 23% of those patients with abnormal leg scans are shown by venography to have extension of the thrombus into the veins of the thigh (21). Pulmonary embolism occurred in almost 40% of the patients when the thigh veins were involved. When only the calf veins were involved, the risk was minimal (21).

**Knowing the Risk of Deep Venous Thrombosis, What is the Risk, if Untreated, of Pulmonary Embolism?**

Few studies directly address this issue, and these are old. The data seem compelling, however. Among 347 untreated patients with clinical evidence of thrombophlebitis, 37% died of pulmonary embolism (22). The risk of recurrent pulmonary embolism is equally grim among untreated patients. Among 19 untreated patients with pulmonary embolism, ten (53%) suffered a recurrent embolism and five (26%) died (23). The indication for prevention and treatment of thromboembolism, therefore, is clear.

**Prevention of Deep Venous Thrombosis**

Low-dose heparin (10,000 to 15,000 units daily, administered subcutaneously in divided doses) has gained wide acceptance as prophylaxis for the prevention of deep venous thrombosis, based upon a multicenter trial of patients undergoing general surgery including abdominal surgery, genitourinary surgery, and some orthopedic surgery (but no thoracic surgery) (20). Among 667 untreated patients and 625 treated patients, the incidence of deep venous thrombosis was reduced from 24.6% to 7.7% with low-dose heparin. This experience seems to be consistent based upon pooled data as reviewed by Sasahara et al (17). A 25% incidence of deep venous thrombosis was reported among 1,884 untreated patients, whereas only 6% of 1,790 treated patients suffered deep venous thrombosis (17). In view of these excellent results, the data have been extrapolated by many physicians to include prophylaxis of other groups of patients at risk of deep venous thrombosis and pulmonary embolism (24). Such intuitive extensions of the data may not be valid.
What About the Use of Low-Dose Heparin Following Orthopedic Surgery, Thoracic Surgery, or Medical Conditions?

The data in this regard are less extensive. Among patients with femoral fractures, a trend suggested some benefit, but the incidence of deep venous thrombosis remained at high levels despite treatment. Among untreated patients, 43% suffered deep venous thrombosis, whereas among those treated with low-dose heparin, 23% had deep venous thrombosis (25). The incidence of pulmonary embolism following hip surgery or above-the-knee amputation was not reduced by low-dose heparin (26). Similarly, following thoracotomy, low-dose heparin reduced the incidence of deep venous thrombosis but was not entirely effective. In such patients, 51% of controls had deep venous thrombosis and 28% of patients treated with low-dose heparin developed deep venous thrombosis (19).

Regarding medical indications for prophylaxis against deep venous thrombosis, heparin has been shown to be beneficial in patients following acute myocardial infarction. In such subjects, pooled data indicate that the incidence of deep venous thrombosis was reduced from 24% in the untreated group to 7% among those who received low-dose heparin (17).

The role of low-dose heparin for the reduction of deep venous thrombosis following nonhemorrhagic stroke looks promising. Using low-dose heparin, the occurrence of deep venous thrombosis on leg scans was decreased from 73% to 22% (27). Of the untreated patients who died, 70% had some pulmonary emboli at autopsy. Immobilization due to malignant conditions has not been studied sufficiently to permit a recommendation regarding low-dose heparin (28).

Antiplatelet Agents

Antiplatelet agents generally have not been effective for the prevention of deep venous thrombosis. Several reports suggest no reduction of deep venous thrombosis with the use of either aspirin or hydroxychloroquine following general surgery. (Hydroxychloroquine is not currently used, however, as an antiplatelet agent.) Pooled data among both treated and untreated groups showed a 21% to 23% incidence of deep venous thrombosis (17). Following hip surgery, however, some have shown an advantageous trend among patients treated with aspirin, with a 45% incidence among untreated patients and a 25% incidence of deep venous thrombosis among patients treated with aspirin (29). Alfaro et al (30) found even better results, although with fewer patients.

The Role of Dextran

Dextran inhibits platelet function and fibrin polymerization. It was not as effective as low-dose heparin for the prevention of deep venous thrombosis following major surgery, but the incidence was improved over untreated controls (31). The incidence of deep venous thrombosis in control subjects, those treated with dextran, and those treated with heparin was 37%, 25%, and 12%, respectively. This experience seems to be confirmed by pooled data which showed a 22% incidence of deep venous thrombosis in control subjects and a 14% incidence among those treated with dextran (17).

Following orthopedic surgery, a reduction of the incidence of deep venous thrombosis was suggested by pooled data which showed a 47% incidence among untreated patients and a 25% incidence among those who received dextran (17).

Ultralow-Dose Heparin for the Prevention of Deep Venous Thrombosis

The use of intravenously administered heparin, 1 U/kg/hr, effectively reduced the occurrence of deep venous thrombosis among 50 untreated patients (22% incidence) and 45 treated patients (4% incidence) (32). There seem to be no confirmatory studies of this observation.

The Role of Pneumatic Compression for Prevention of Deep Venous Thrombosis

Intermittent pneumatic leg compression is thought to activate the fibrinolytic system as well as prevent stasis. Following general surgery, intermittent pneumatic compression appears effective, reducing the incidence of deep venous thrombosis from 29% to 3% (17). Among patients following neurosurgery, intermittent pneumatic compression reduced the incidence of deep venous thrombosis from 19% to 1.5% in one study (33) and from 25% to 9% in another (34).

The Risk of Preventive Treatment

Low-dose heparin is contraindicated in patients undergoing operations on the eye or brain (35). An increased number of wound hematomas following low-dose heparin in patients undergoing abdominal or thoracic surgery has been reported, but no differences were noted in the number of deaths attributable to hemorrhage. Some investigators have observed increased bleeding and wound complications following therapy with low-dose heparin (36). Thrombocytopenia also has been reported with low-dose heparin (37,38).

The question of complications with low-dose heparin was addressed in detail in a survey (24). Of the 83 cardiologists and pulmonary physicians who responded, some were directors of coronary care or intensive care units at major hospitals and consequently had seen hundreds of patients treated with low-dose heparin. Most physicians (90%) recalled no complications other than a rare and clinically unimportant hematoma at the site of injection. Heparin in low doses, in the absence of a contraindication, therefore, would seem safe. A few physicians, however, have encountered complications. Massive hematomas of the abdominal wall occurred in two patients. One of these patients also suffered thrombocytopenia induced by heparin. Wound infection and sepsis developed, and the patient died. (This was the only reported death related to low-dose heparin.) Thrombocytopenia was induced by heparin in three other patients. Bleeding from wounds severe enough to require a blood transfusion occurred in three patients. Bleeding at a distal site, usually gastrointestinal (some of which may have been secondary to stress ulcers), was observed in six patients. The preva-
Risks of Treatment of Deep Venous Thrombosis and Pulmonary Embolism

Treatment of patients with deep venous thrombosis for 12 weeks with warfarin at a prothrombin time of 1.5 to 2 times control after two weeks of treatment with heparin resulted in a recurrence rate of deep venous thrombosis of only 2%, which was comparable to heparin therapy among patients in whom the partial thromboplastin time was 1.5 to 2 times control (39). Bleeding occurred in 17% of patients treated with warfarin but only in 1% treated with heparin.

Initial heparin requirements are greater and heparin clearance more rapid in patients with deep venous thrombosis and pulmonary embolism than in controls (40). Following the same dose of heparin (7,750 units) in controls and patients with deep venous thrombosis, the partial thromboplastin time was 20 seconds shorter in those with deep venous thrombosis. More heparin, therefore, was required to maintain the same therapeutic partial thromboplastin time.

Low-dose heparin (5,000 units every 12 hours) is ineffective in the treatment of deep venous thrombosis. Among 35 patients with deep venous thrombosis who were treated for three months with low-dose heparin, deep venous thrombosis occurred in 23% and pulmonary embolism occurred in 3% (41). Among 33 patients with deep venous thrombosis who were treated with warfarin (prothrombin time 1.5 to 2 times control), there was no recurrence or pulmonary embolism (41). Bleeding complications, however, were greater among patients treated with warfarin.

The duration of anticoagulant therapy reasonably can be kept to 12 weeks because thromboembolic complications are relatively infrequent after that time (42). More recent data suggest that even six weeks of therapy is as effective as more prolonged therapy in preventing recurrent venous thrombosis or pulmonary embolism (43).

The risk of bleeding with warfarin increases with the duration of therapy. Some have reported a 10% risk of major bleeding with 12 weeks, 18% with one year, 26% with two years, and 41% with five years (43). This is higher than the reported incidence of bleeding among patients anticoagulated because of myocardial infarction or prosthetic heart valves. The reported incidence in such patients ranged from two to 15 per 100 patients per year, and the incidence of major bleeds was zero to eight per 100 patients per year (44). Because of the high incidence of bleeding with intense warfarin therapy, the use of less intense warfarin has been explored.

In patients undergoing hip and knee replacement, Francis et al (45) administered warfarin to prolong the prothrombin time to about 1.1 to 1.2 times control before surgery and kept it at 1.5 times control or less after surgery. This reduced the incidence of deep venous thrombosis to 21% in comparison to deep venous thrombosis in patients treated with dextran (51%). In the treatment of patients with deep venous thrombosis, Hull et al (46) found the same incidence (2%) of recurrent deep venous thrombosis and/or pulmonary embolism with less intense warfarin (prothrombin time 1.4 to 2 times control) that they observed with more intense warfarin (prothrombin time 1.8 times control). Others also employed a comparable intensity level of warfarin with success. Deep venous thrombosis was 6% following major gynecological surgery in patients treated with oral anticoagulants with a prothrombin time equivalent to that of rabbit brain thromboplastin (1.3 to 1.8 times control) (47). Sevitt and Gallagher (48), with oral anticoagulants administered to produce a prothrombin time equivalent to that of rabbit brain thromboplastin of 1.3 to 1.5 times control, reduced the incidence of pulmonary embolism in patients following hip fracture from 18% in controls to zero in treated patients. In the prevention of recurrent pulmonary embolism, Coon and associates (42), with less intense warfarin (prothrombin time 1.4 to 1.8 times control), showed a recurrence of pulmonary embolism of 7%, whereas with more intense warfarin (prothrombin time 1.9 to 2.8) the recurrence of pulmonary embolism was 3%.

All reported measurements of the prothrombin time in this review give measurements or equivalent measurements that would be obtained with a one-stage prothrombin time obtained with rabbit brain thromboplastin. Hirsh et al (49) described that the prothrombin time measured with rabbit brain thromboplastin (as is typical in the United States and Canada) would be less prolonged than the prothrombin time measured with human brain thromboplastin (as is typical in the United Kingdom). A prothrombin time of 2 times control obtained with human brain thromboplastin is equivalent to a prothrombin time of 1.2 to 1.3 times control with rabbit brain thromboplastin. This important difference may have led physicians in North America to misinterpret reports from the United Kingdom. For example, Sevitt and Gallagher (48), when reporting good results in the prevention of deep venous thrombosis in patients with fractures, indicated that they achieved a prothrombin time of 2 to 3 times control using human brain thromboplastin. In the United States, with rabbit brain thromboplastin, this would be an equivalent prothrombin time of 1.3 to 1.5 times control. If, through misinterpretation, physicians in the United States achieved a prothrombin time of 2 to 3 times control, it would be as if Sevitt and Gallagher employed a prothrombin time that exceeded safe levels.

Pulmonary Embolism

The risk of fatal pulmonary embolism is greater among patients who have had an episode of pulmonary embolism than in those with deep venous thrombosis (39). Despite anticoagulant therapy, fatal recurrent pulmonary embolism occurred in 1% of those with a previous pulmonary embolism but in only 0.1% of the patients with deep venous thrombosis and no previous pulmonary embolism.

Recommendations for Prevention of Venous Thromboembolism

Recommendations of the American College of Chest Physicians—National Heart, Lung, and Blood Institute National Conference on Antithrombotic Therapy (50) are paraphrased as follows:

1. Moderate risk patients (general and gynecological surgery, medical patients, and presumably thoracic surgery): 5,000 units
of heparin subcutaneously every 12 hours or intermittent pneumatic compression.

2. Patients undergoing neurosurgery, major knee surgery, or urologic surgery: treatment with intermittent pneumatic compression.

3. Patients undergoing elective hip surgery: pretreat with adjusted dose of heparin (activated partial thromboplastin time in upper half of normal range), or treat with moderate dose of warfarin (prothrombin time 1.2 to 1.5 times control).

4. Patients undergoing surgery for fractured hip: moderate dose of warfarin (prothrombin time 1.2 to 1.5 times control).

Comments

The strength of the aforementioned recommendations is clear from the data presented in the Table, which represent pooled results from numerous studies, most of which are referenced in the text. This Table, therefore, serves only as a guideline. It is apparent from the Table that most forms of prophylaxis have some benefit, although the level of protection afforded by each varies with the clinical circumstances. Therefore, if a particular form of prophylaxis may not be appropriate for an individual patient, any of the various regimens may offer some measure of protection.

Recommendations for the Treatment of Venous Thrombosis or Pulmonary Embolism

1. First episode: intravenous heparin or subcutaneous heparin sufficient to prolong the activated partial thromboplastin time 1.5 to 2 times control.
2. Continue heparin seven to ten days.
3. Overlap with oral anticoagulants at least five days.
4. Continue oral anticoagulants for three months.
5. Maintain warfarin at prothrombin time 1.2 to 1.5 times control.

If there is a recurrent or continuing risk of deep venous thrombosis or pulmonary embolism, indefinite duration of anticoagulants is recommended. If only the calf veins are involved, no treatment may be necessary if serial impedance plethysmography is negative, or heparin may be administered followed by warfarin for six weeks.

These and future guidelines undoubtedly will be modified as further prospective studies are documented.

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References

Anticoagulant and Antithrombotic Therapy—Stein