HEPARIN FOR 5 DAYS AS COMPARED WITH 10 DAYS IN THE INITIAL TREATMENT OF PROXIMAL VENOUS THROMBOSIS

RUSSELL D. HULL, M.B.B.S., M.Sc., GARY E. RASKOB, M.Sc., DAVID ROSENBLOOM, PHARM.D., AKBAR A. PANJU, M.B.Ch.B., PATRICK BRILL-EDWARDS, M.D., JEFFREY S. GINSBERG, M.D., JACK HIRSH, M.D., GARY J. MARTIN, M.D., AND DAVID GREEN, M.D., PH.D.

Abstract It is common practice to begin anticoagulant treatment of deep-vein thrombosis with a 10-day course of intravenous heparin, with warfarin added on day 5 to 10 and continued for several months. We performed a randomized, double-blind trial comparing a shorter course of continuous intravenous heparin (5 days, with warfarin sodium begun on the first day) with the conventional 10-day course of heparin (with warfarin sodium begun on the fifth day) in the initial treatment of 199 patients with acute proximal venous thrombosis documented by venography.

The frequency of objectively documented recurrent venous thromboembolism was low and essentially the same in the two groups (7.1 percent in the short-course group vs. 7.0 percent in the long-course group). Because the observed difference between the groups was 0.1 percent in favor of the long-course group, it is unlikely ($P<0.05$) that a true difference in favor of this group would be greater than 7.5 percent; the difference could be as much as 7.3 percent in favor of the short-course group. Major bleeding episodes were infrequent, and the rate was similar in both groups.

We conclude that a five-day course of heparin is as effective as a 10-day course in treating deep venous thrombosis. Furthermore, using the shorter course would permit earlier discharge from the hospital and thus offer substantial cost savings. (N Engl J Med 1990; 322:1260-4.)

IN recent years improvements in the methods of clinical trials and the use of accurate objective tests to detect venous thromboembolism[1-6] have made it possible to perform a series of randomized trials to evaluate various treatments for venous thromboembolism.[7-14] The results of these trials[7-14] have resolved many of the uncertainties that a clinician confronts in selecting an appropriate course of anticoagulant therapy. These trials have shown, for example, that the intensity of initial heparin treatment and long-term anticoagulant therapy must be sufficient to prevent unacceptable rates of recurrence of venous thromboembolism.[11,14] Patients with proximal deep-vein thrombosis who receive inadequate anticoagulant therapy have a risk of recurrent venous thromboembolism that approaches 50 percent.[11] Although both the need for anticoagulant therapy[11,14] and the importance of monitoring blood levels of anticoagulant effect[13,14] have been established, the ideal duration of initial treatment remains uncertain.

The conventional approach is to give the patient heparin for 10 days, beginning oral anticoagulant therapy on day 5 to 10 to ensure a crossover period of 4 to 5 days before heparin is discontinued. The rationale for this regimen was initially based on observations in animals[15-17]; subsequently, clinical trials have demonstrated its effectiveness.[7,14] More recently, because of the desirability of shortening the hospital stay, heparin therapy has been reduced to five days in many hospitals; this practice has been encouraged in the United States by the method of paying for medical care according to diagnosis-related groups.[18] The scientific data supporting the use of a shorter course of heparin treatment are limited to the results of one open-label, randomized study that evaluated outcomes in patients with less than massive venous thromboembolism.[19]

The use of short courses of heparin has gained widespread acceptance because of economic factors, despite the lack of firm data supporting the effectiveness of this form of treatment. For this reason, we undertook a double-blind, randomized trial comparing a short course of heparin administered by continuous intravenous infusion (5 days), in which oral anticoagulant therapy was instituted on the first day, with the traditional long course of heparin (10 days), in which oral anticoagulant treatment was begun on the fifth day, in the initial treatment of patients with acute proximal deep-vein thrombosis. Our study sought to determine the relative effectiveness of these two regimens and the risk of bleeding associated with them.

METHODS

Patients

Those enrolled in the study were consecutive patients referred to Chedoke–McMaster Hospitals with proximal deep-vein thrombosis documented by venography.[1,3] Patients were excluded if they had active bleeding or disorders contraindicating anticoagulant therapy (15 patients); if they had received heparin intravenously for more than 24 hours (11); if they could not be followed up because of geographic inaccessibility (22); or if they declined to give informed consent (44). Before randomization, the patients were stratified into groups according to whether or not they had a history of venous thrombosis and according to the absence (low risk) or presence (high risk) of one or more risk factors for bleeding (surgery within the previous 14 days; a history of peptic-ulcer disease, bleeding into the gastrointestinal or genitourinary tract, or disorders predisposing the patient to bleeding; thrombotic stroke within the previous 14 days; or a platelet count $<150\times10^9$ per liter). A randomized treat-

From the Section of Medicine (A.A.P., P.B.-E., J.S.G., J.H.) and the Department of Pharmaceutical Services (D.R.), Chedoke–McMaster Hospitals, McMaster University, Hamilton, Ont.; the Sections of General Internal Medicine (G.J.M.) and Hematology/Oncology (D.G.), Department of Medicine, Northwestern Memorial Hospital and Northwestern University Medical School, Chicago; and the Clinical Trials Unit, Division of General Internal Medicine, University of Calgary, Calgary, Alb. (R.D.H., G.E.R.). Address reprint requests to Dr. Hull at the University of Calgary, Department of Medicine, Foothills Hospital, 3330 Hospital Dr., N.W., Calgary, AB T2N 4N1, Canada.

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ment schedule (derived by computer) was used to assign patients to either 10 days of intravenous heparin treatment (long-course group) or 5 days of such treatment (short-course group).

Regimens

All patients received an intravenous bolus of 5000 USP units of heparin, followed by a continuous intravenous infusion of heparin. The initial dose was 40,000 units per 24 hours for patients classified as being at low risk for bleeding and 30,000 units per 24 hours for high-risk patients. These doses were chosen to minimize the risk of inadequate heparin treatment during the first 24 hours of therapy.[14] The patients were allowed to move around as they wished once the activated partial thromboplastin time indicated a therapeutic response.

A double-blind study design was used because knowledge of the patient's treatment group might have influenced the intensity of the search for subsequent events or the selection and intensity of ancillary therapy.[20] Patients in the long-course group received heparin intravenously for 10 days. Patients in the short-course group received heparin intravenously for five days, then an intravenous placebo infusion for five days. In patients assigned to receive the short course of heparin, treatment with warfarin sodium was begun on the first day. In patients assigned to the long course, treatment with warfarin sodium began on the fifth day; these patients received placebo capsules identical in appearance to the warfarin capsules on days 1 through 4. The initial dose of warfarin sodium was 10 mg in all patients.

Monitoring of heparin and warfarin sodium treatment by laboratory testing was identical in both groups and is described in detail elsewhere.[13,14] The activated partial thromboplastin time was measured four hours after the beginning of intravenous heparin treatment; the test was repeated at intervals of four to six hours until the result was within the prescribed therapeutic range (1.8 to 2.8 times the mean normal control value of 30 seconds when Actin-Fs thromboplastin reagent [Dade] was used). Thereafter, the activated partial thromboplastin time was measured once daily. The dose of warfarin sodium was adjusted daily, with the prothrombin time used to maintain the international normalized ratio between 2.0 and 3.0.[13,21] In both groups, an international normalized ratio of at least 2.0 was a requirement for discontinuing the heparin infusion.

In order to maintain blinding as to the patient's treatment group, the activated partial thromboplastin time and prothrombin time were reported only to a clinical pharmacist, who was not involved in the assessment of the patient's outcome, and were not recorded on the patient's chart during the study or reported to any other member of the health care team. Adjustments in the rate of infusion of heparin or placebo or the dose of warfarin sodium or placebo capsules were made by the nursing staff, on the basis of the recommendations of the clinical pharmacist, according to dosage schedules established before the trial began.

Treatment with warfarin sodium was continued for 12 weeks in both groups. After the first 10 days, the dose of warfarin sodium was adjusted weekly by the patients' primary physicians, who agreed to maintain the international normalized ratio between 2.0 and 3.0.[13,14]

The use of aspirin-containing drugs, sulfinpyrazone, dipyridamole, and thrombolytic agents was prohibited during the trial. Adherence to the study regimens was monitored during hospitalization by reviews of the patients' charts.

Surveillance and Follow-up

All the patients were examined daily during the first 10 days; they were then followed for three months.[14] The patients were asked to come to the hospital immediately if symptoms or signs of recurrent deep-vein thrombosis or pulmonary embolism developed. In addition, all the patients were assessed 3, 6, and 12 weeks after the initial heparin therapy and underwent objective testing as described previously.[11-14] Patients with suspected recurrent venous thrombosis underwent impedance plethysmography, leg scanning, and venography; diagnostic criteria are described elsewhere.[1,4,11-14] In patients in whom pulmonary embolism was suspected on the basis of clinical signs or symptoms, the diagnosis was confirmed either by lung-scan findings indicating a high probability of pulmonary embolism[6,22] or by pulmonary angiography,[5,6,23] which was performed in patients in whom lung scanning did not indicate a high probability of pulmonary embolism.

Bleeding was classified as major or minor according to criteria described previously.[11-14]

Statistical Analysis

Fisher's exact test was used to compare the frequency of recurrent venous thromboembolism and bleeding in the two treatment groups. Confidence limits for the true incidence of recurrent venous thromboembolism and bleeding complications were calculated from the binomial distribution. Confidence limits for the difference in the incidence of recurrent venous thromboembolism and bleeding complications between the two treatment groups were calculated with use of the normal approximation to the binomial distribution.

Results

Patients

One hundred ninety-nine consecutive patients were enrolled in the study; the treatment groups were comparable at entry (Table 1). All 199 patients were followed during initial therapy and for three months during long-term therapy; none were lost to follow-up.

Recurrent Venous Thromboembolism

Seven of the 100 patients who received the long course of heparin (7.0 percent; 95 percent confidence interval, 2.9 to 13.9) and 7 of the 99 patients who received the short course (7.1 percent; 95 percent confidence interval, 2.9 to 14.0) had new episodes of symptomatic venous thromboembolism that were documented by objective testing. These patients presented with overt symptoms and signs of throm-

Table 1. Clinical Characteristics of 199 Patients with Proximal Venous Thrombosis Treated with a Long Course (10 Days) or a Short Course (5 Days) of Intravenous Heparin.

Characteristic	Treatment Group	
	Long course	Short course
	no. of patients	
Total no.	100	99
Age (<60 yr/≥60 yr)	23/77	21/78
Sex (M/F)	48/52	46/53
Status on entry		
Thrombosis suspected clinically	38	40
Thrombosis detected by screening*	62	59
History of deep-vein thrombosis	15	16
Underlying disorders or surgery		
Hip operation	39	39
Knee operation	10	7
Idiopathic deep-vein thrombosis	25	28
Congestive heart failure	2	0
Cancer	7	6
Paralysis of leg	6	6
Miscellaneous	11	13
Risk of bleeding		
High	58	53
Low	42	46

*In patients judged to be at risk for venous thrombosis.

boembolism. Since the observed difference in incidence between the groups was 0.1 percent in favor of the long-course group, it is unlikely ($P<0.05$) that a true difference in favor of this group would be greater than 7.5 percent, and the difference could be as much as 7.3 percent in favor of the short-course group.

Of the seven patients in the long-course group who had new episodes of venous thromboembolism, one had pulmonary embolism (confirmed by pulmonary angiography) presenting as pleuritic chest pain of new onset, and six had recurrent deep-vein thrombosis (Table 2). Recurrent venous thrombosis was documented by venography in three of the six patients, who were found to have new constant proximal intraluminal filling defects. In the remaining three patients, recurrent venous thrombosis was documented by impedance plethysmography (two patients) and leg scanning with use of ^{125}I-labeled fibrinogen (one patient); two of the three patients had grossly abnormal venograms with collateral veins and poor filling of venous segments, and the remaining patient refused repeat venography.

Seven patients in the short-course group also had recurrent venous thrombosis (Table 2). Venography documented new constant intraluminal filling defects in the proximal veins of two of the seven patients, and recurrent venous thrombosis was documented in the remaining five patients by impedance plethysmography (four of these five had grossly abnormal venograms with collateral veins and poor filling of venous segments, and the remaining patient refused repeat venography).

Table 2. Recurrent Venous Thromboembolic Events in the Two Groups.

Event	Time after Start of Heparin (days)	INR*	Underlying Disorder or Surgery
Long-course group (n = 7)			
Pulmonary embolism	17	2.4	Hip surgery
Deep-vein thrombosis	21	1.7	Idiopathic deep-vein thrombosis
Deep-vein thrombosis	22	2.4	Previous deep-vein thrombosis
Deep-vein thrombosis	24	1.5	Cancer
Deep-vein thrombosis	37	1.7	Knee surgery, previous deep-vein thrombosis
Deep-vein thrombosis	53	2.7	Knee surgery, previous deep-vein thrombosis
Deep-vein thrombosis†	70	—	Hip surgery
Short-course group (n = 7)			
Deep-vein thrombosis	21	1.7	Hip surgery
Deep-vein thrombosis	27	2.7	Paralysis of leg, previous deep-vein thrombosis
Deep-vein thrombosis	28	1.7	Idiopathic deep-vein thrombosis
Deep-vein thrombosis	30	3.1	Idiopathic deep-vein thrombosis
Deep-vein thrombosis‡	50	1.6	Transurethral prostatectomy, paralysis of leg
Deep-vein thrombosis	52	3.1	Paralysis of leg
Deep-vein thrombosis‡	53	—	Cancer

*INR denotes international normalized ratio.

†Long-term heparin therapy was withheld because of major bleeding.

‡Long-term heparin therapy was interrupted because of major bleeding.

Bleeding Complications

Hemorrhagic complications occurred during initial heparin therapy in 12 of the 100 patients treated with the long course of heparin (12.0 percent; 95 percent confidence interval, 6.4 to 20.0) and in 9 of the 99 patients given the short course (9.1 percent; 95 percent confidence interval, 4.2 to 16.6) (Table 3). Since the observed difference in incidence between the groups was 2.9 percent in favor of the short-course group, the difference in favor of this group could be as much as 11.5 percent, and it is unlikely ($P<0.05$) that a true difference would be greater than 6.4 percent in favor of the long-course group.

Major bleeding complications occurred in 6 of the 100 patients who received the long course of heparin (6.0 percent; 95 percent confidence interval, 2.2 to 12.6) and in 7 of the 99 patients who received the short course (7.1 percent; 95 percent confidence interval, 2.9

Table 3. Bleeding Complications during Initial Heparin Treatment in the Two Groups.*

Site of Bleeding	Time after Start of Heparin (days)	Predisposing Condition or Surgery	APTT (sec)	INR
Long-course group (n = 12)				
Major bleeding (n = 6)				
Thigh	2	Hip surgery	>110	—
Thigh	2	Hip surgery	56	—
Retroperitoneum	2	Hip surgery	93	—
Thigh	3	Hip surgery	69	—
Retroperitoneum	4	Abdominal surgery	64	—
Upper gastrointestinal tract	5	Peptic ulcer	92	2.3
Minor bleeding (n = 6)				
Epistaxis	1	—	68	—
Rectum	4	Hemorrhoids	49	—
Thigh	5	—	105	1.5
Upper gastrointestinal tract	5	Gastric ulcer	89	2.7
Vagina	8	—	99	2.0
Rectum	9	Radiation proctitis	80	3.1
Short-course group (n = 9)				
Major bleeding (n = 7)				
Upper gastrointestinal tract†	1	Gastric erosions, uremia, thrombocytopenia	>110	1.2
Thigh‡	1	Hip surgery	>110	10.0
Thigh	2	Hip surgery	58	2.7
Rectum	3	Large-bowel surgery	76	3.1
Rectum	3	Ulcerative colitis	64	1.7
Retroperitoneum	4	Renal-cell carcinoma	93	3.6
Prostate	5	Transurethral prostatectomy	>110	2.7
Minor bleeding (n = 2)				
Hematuria	1	Urethral catheter	78	1.4
Thigh	2	Hip surgery	80	4.5

*APTT denotes activated partial thromboplastin time, and INR international normalized ratio.

†Warfarin sodium was not given; bleeding began three hours after the initiation of heparin treatment.

‡A large thigh hematoma was present at the onset of therapy and subsequently continued to bleed. The INR was 10.0 on day 2.

to 14.0). Since the observed difference in the incidence of major bleeding between the groups was 1.1 percent in favor of the long-course group, it is unlikely ($P<0.05$) that a true difference in favor of this group would be greater than 8.0 percent, and the difference could be as much as 6.3 percent in favor of the short-course group.

The mean decrease in the hemoglobin level was 1.3 mmol per liter (2.11 g per deciliter) in the short-course group and 1.2 mmol per liter (1.99 g per deciliter) in the long-course group ($P>0.10$). The mean number of units of packed red cells transfused was 2.44 in the short-course group and 1.75 in the long-course group ($P>0.10$).

The bleeding complications observed during initial heparin treatment were analyzed according to the criteria for high or low risk of bleeding that were assigned before the study began (Table 4). Only eight patients (4 percent) had bleeding during long-term therapy with warfarin sodium — three in the long-course group (two of whom had major bleeding) and five in the short-course group (two of whom had major bleeding). In one patient in the short-course group, minor bleeding began the day after heparin was discontinued; the remainder of the episodes occurred between 2 and 11 weeks after the beginning of long-term therapy.

Table 4. Frequency of Bleeding Complications during Initial Heparin Treatment, According to Risk of Bleeding.*

Category	Treatment Group	
	Long course	Short course
	no. with bleeding/no. in category (%)	
Major bleeding†		
High-risk patients	6/58 (10)	6/53 (11)
Low-risk patients	0/42 (0)	1/46 (2)
Minor bleeding		
High-risk patients	2/58 (3)	1/53 (2)
Low-risk patients	4/42 (10)	1/46 (2)

*Patients were classified at entry as being at high or low risk of bleeding.

†Major bleeding occurred in 1 of 88 low-risk patients (1 percent) as compared with 12 of 111 high-risk patients (11 percent; $P = 0.007$).

Deaths

Eight patients in the short-course group and two in the long-course group died during initial heparin therapy ($P = 0.058$; Table 5). The cause of death was determined by personnel who had no knowledge of the patient's treatment group. One patient had major bleeding three hours after heparin therapy began and died later as a result of acute renal failure; because of the bleeding, warfarin sodium therapy was not administered to this patient. The other patient, who had had hip surgery, had a large wound hematoma before heparin was initiated, subsequently continued to bleed, and died of an acute myocardial infarction.

Other Findings

Two of the 100 patients in the long-course group (2.0 percent) and 3 of the 99 patients in the short-course group (3.0 percent) had thrombocytopenia (platelet count $<150\times10^9$ per liter) during heparin treatment. Two patients (both in the short-course group) had other factors that cause thrombocytopenia (vinblastine treatment and septicemia). No patient had warfarin-induced skin necrosis.

Discussion

The primary objective of this study was to determine whether initial heparin therapy could be shortened to five days without loss of effectiveness. The frequency of objectively documented recurrent venous thromboembolism was low in each group (7 percent). The low frequency of this complication in both groups is in striking contrast to the results obtained in our previous randomized study,[14] in which inadequate initial heparin therapy was associated with a 25 percent risk of recurrent venous thromboembolism. Both studies used the same design, both compared different heparin regimens with long-course heparin therapy, and both were carried out in the same referral center.

The frequency of bleeding complications (both major and minor) was 9.1 percent in the short-course group and 12.0 percent in the long-course group. Thrombocytopenia occurred infrequently in each patient group.

Care was taken to ensure that bias did not influence the outcomes observed in the study. Patients were randomly assigned to treatments, and the two groups were comparable at entry, confirming the absence of bias in treatment assignment. A double-blind study design was used, since knowledge of the patients' treatment groups might have influenced the detection of events[20] as well as the selection and intensity of ancillary therapy.[20] Thus, our results cannot be attributed to bias.

Major hemorrhagic complications occurred in only 1 percent of the patients classified as being at low risk

Table 5. Causes of Death in the Two Groups.

Cause of Death	Long-Course Group (N = 2)		Short-Course Group (N = 8)	
	No. of Patients	Days after Randomization	No. of Patients	Days after Randomization
Death during initial therapy				
Thigh hematoma, myocardial infarction*	0	—	1	3
Gastrointestinal bleeding, uremia†	0	—	1	3
Death during long-term therapy				
Aspiration pneumonia, congestive heart failure, complete heart block	0	—	1	16
Septicemia	1	58	2	20, 30
Myocardial infarction	1	48	0	—
Disseminated carcinoma	0	—	2	36, 64
Renal tubular acidosis, renal failure	0	—	1	62

*A large thigh hematoma was present at the onset of therapy.

†Warfarin sodium was not administered because of bleeding.

for bleeding, as compared with 11 percent of the patients at high risk for bleeding ($P = 0.007$) (Table 4). All the patients with major bleeding episodes had an underlying predisposing cause (Table 3). Two patients had major bleeding the day before they died. Both were considered at high risk of bleeding, and both were in the short-course group; one patient had bleeding three hours after the beginning of heparin therapy and therefore did not receive any warfarin sodium, and the other had an extensive thigh hematoma before heparin was begun. In patients at extremely high risk of bleeding (for example, patients who have just had surgery, those in the intensive care unit with multiple invasive lines, or those who have conditions that predispose them to major bleeding), it would be prudent to delay oral anticoagulant treatment, since the effect of heparin can be reversed almost instantly, but it may take six to eight hours to reverse the effect of oral anticoagulant agents.

Because our study had a double-blind design, all the patients remained in the hospital for the same length of time. Thus, it was not possible to measure directly the number of hospital days that could be saved by using short-course heparin treatment (to do so might have biased the evaluation of outcome because of loss of blinding as to the patients' treatment-group assignments). Because the room costs are an important component of in-hospital expenditures and because venous thromboembolism is a common disorder, the use of short-course heparin therapy has the potential to lead to enormous savings. In the United States, the potential savings has been estimated to be approximately $500 million (in 1986 dollars), assuming that 300,000 patients with venous thromboembolism are treated each year.[18] In an era of fiscal constraint, a short course of heparin is an effective treatment that offers a substantial financial benefit without detracting from the patient's care.

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