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A COMPARISON OF LOW-MOLECULAR-WEIGHT HEPARIN ADMINISTERED PRIMARILY AT HOME WITH UNFRACTIONATED HEPARIN ADMINISTERED IN THE HOSPITAL FOR PROXIMAL DEEP-VEIN THROMBOSIS

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Abstract Background. Patients with acute proximal deep-vein thrombosis are usually treated first in the hospital with intravenous standard (unfractionated) heparin. However, the longer plasma half-life, better bioavailability after subcutaneous administration, and more predictable anticoagulant response of low-molecular-weight heparins make them attractive for possible home use. We compared these two approaches.

Methods. Patients with acute proximal deep-vein thrombosis were randomly assigned to receive either intravenous standard heparin in the hospital (253 patients) or low-molecular-weight heparin (1 mg of enoxaparin per kilogram of body weight subcutaneously twice daily) administered primarily at home (247 patients). The study design allowed outpatients taking low-molecular-weight heparin to go home immediately and hospitalized patients taking low-molecular-weight heparin to be discharged early. All the patients received warfarin starting on the second day.

Results. Thirteen of the 247 patients receiving low-molecular-weight heparin (5.3 percent) had recurrent thromboembolism, as compared with 17 of the 253 patients receiving standard heparin (6.7 percent; $P = 0.57$; absolute difference, 1.4 percentage points; 95 percent confidence interval, -3.0 to 5.7). Five patients receiving low-molecular-weight heparin had major bleeding, as compared with three patients receiving standard heparin. After randomization, the patients who received low-molecular-weight heparin spent a mean of 1.1 days in the hospital, as compared with 6.5 days for the standard-heparin group; 120 patients in the low-molecular-weight-heparin group did not need to be hospitalized at all.

Conclusions. Low-molecular-weight heparin can be used safely and effectively to treat patients with proximal deep-vein thrombosis at home. (N Engl J Med 1996;334:677-81.)

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PATIENTS with acute proximal deep-vein thrombosis are usually treated initially in the hospital with standard (unfractionated) heparin, administered by continuous intravenous infusion for five to seven days.¹ The anticoagulant response to this treatment varies markedly among patients, and therefore the dosage must be monitored by measuring the activated partial-thromboplastin time closely.^{1,2}

Low-molecular-weight heparins, which are prepared by the depolymerization of standard heparin, have proved to be safe and effective in preventing thromboembolism in patients at high risk³ and to be at least as safe and ef-

fective as standard heparin for the treatment of acute proximal deep-vein thrombosis.^{4,6} In these trials, standard heparin was administered by continuous intravenous infusion, and the dosage was adjusted to keep the activated partial-thromboplastin time within a prescribed range. In contrast, the low-molecular-weight heparins were administered by subcutaneous injection in doses adjusted for the patient's weight, without laboratory monitoring. This more convenient method of administering the treatment is possible because low-molecular-weight heparins have a more predictable anticoagulant response than standard heparin, a longer plasma half-life, and better bioavailability when administered subcutaneously.⁷⁻⁹

Because of these properties, low-molecular-weight heparins have the potential advantage of allowing patients with proved deep-vein thrombosis to be treated at home rather than in the hospital. We carried out a randomized trial in patients with acute deep-vein thrombosis that compared the use of continuous intravenous standard heparin in the hospital with the administra-

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tion of subcutaneous low-molecular-weight heparin primarily at home. Although we encouraged immediate home treatment in the case of outpatients randomly assigned to receive low-molecular-weight heparin, our study design also allowed these patients to be admitted to the hospital briefly and treated with low-molecular-weight heparin if their clinical condition precluded immediate treatment as outpatients but if they were considered to be good candidates for early discharge — that is, within four days. In addition, we included patients with proximal deep-vein thrombosis who had been admitted to the hospital at night or on a weekend, most of whom were initially treated with standard heparin, and patients who had been hospitalized for other reasons but in whom deep-vein thrombosis developed; in all cases, the study patients had to be suitable candidates for early discharge.

METHODS

Study Patients

Consecutive patients in whom acute proximal deep-vein thrombosis (thrombosis involving the popliteal vein or a more proximal vein) had been confirmed by either venography or duplex ultrasonography were eligible for the study. Patients were excluded from the study if they had any of the following: two or more previous episodes of deep-vein thrombosis or pulmonary embolism; currently active bleeding, active peptic ulcer disease, or a familial bleeding disorder; concurrent symptomatic pulmonary embolism; treatment lasting more than 48 hours with standard heparin for the deep-vein thrombosis qualifying them for the study; an inability to be treated with low-molecular-weight heparin as an outpatient because of a coexisting condition (for example, cancer, infection, or stroke) or the likelihood of noncompliance; an inability to make follow-up visits to the clinic because of geographic inaccessibility; the presence of a known deficiency of antithrombin III, protein C, or protein S; or pregnancy.

The study protocol was reviewed and approved by the institutional review boards of the participating centers (see the Appendix). Informed consent was obtained from eligible patients before their assignment to a study treatment.

Study Design

Patients were assigned to undergo treatment with either low-molecular-weight heparin primarily at home or continuous intravenous standard heparin in the hospital through randomization over the telephone from a central site. The randomization was stratified according to center, mode of diagnosis (venography or ultrasonography), and category of patient. The first category of patients included those who presented as outpatients. The second category included patients with deep-vein thrombosis who were admitted at night or on a weekend, who for logistic reasons could not be enrolled in the study immediately and thus were first treated with standard heparin. The third category included patients who were hospitalized for other reasons, such as surgery, and in whom deep-vein thrombosis was subsequently diagnosed.

Treatment Regimens

The patients assigned to therapy with low-molecular-weight heparin received 1 mg of enoxaparin (Rhône-Poulenc Rorer, Montreal) per kilogram of body weight subcutaneously twice daily. The medication was supplied in 1-ml ampules, each containing 100 mg of enoxaparin (100 International Factor Xa Inhibitory Units per milligram). The patient (and a family member, if appropriate) was taught by the study nurse how to administer the study medication subcutaneously. The first dose was given by the patient under the supervision of the nurse. The medication was drawn up into 1-ml plastic syringes (Becton Dickinson, Rutherford, N.J.) similar to those used for insulin injections and was injected through a 28.5-gauge needle. In some in-

stances the study nurse loaded a series of syringes with the study medication and sent the patient home with enough syringes for several days of treatment.

The patients randomly assigned to therapy with standard heparin were admitted to the hospital. They received a bolus dose of 5000 units intravenously, followed by a continuous infusion of 20,000 units of standard heparin in 500 ml of a 5 percent dextrose solution, with 32 ml administered per hour. The activated partial-thromboplastin time was measured 6 hours after heparin therapy began, and the dose rate was adjusted to maintain this variable in the targeted therapeutic range of 60 to 85 seconds with use of a previously published nomogram.¹⁰ This range was equivalent to a heparin level of 0.2 to 0.4 unit per milliliter as measured by titration against protamine. The prothrombin time and activated partial-thromboplastin time of the patients in this group were measured at least once daily.

The patients began to receive warfarin sodium on the evening of the second day of treatment with the study medication. The first dose of warfarin was usually 10 mg. Thereafter, each patient's prothrombin time was measured daily, and warfarin was prescribed to achieve an international normalized ratio of 2.0 to 3.0. In the outpatients, the prothrombin time was measured daily either at the outpatient hospital laboratory or a community laboratory or at the patient's home, by a staff member of a community laboratory. The study medication was discontinued when the targeted therapeutic range for the international normalized ratio was reached and maintained for two consecutive days. However, each patient should have been treated for at least five days with either low-molecular-weight heparin or standard heparin. The study nurse contacted each outpatient daily by telephone to ensure that there were no problems and to adjust the dose of warfarin. Inpatients were seen daily by the study nurse. All the patients were scheduled to receive warfarin for at least three months.

In the case of the patients admitted at night or on a weekend, the first dose of low-molecular-weight heparin was administered 30 to 60 minutes after the discontinuation of the heparin infusion. In this group, the period during which the patient had received standard heparin before randomization was considered part of the overall duration of heparin therapy.

Follow-up and Outcome Measures

All the patients underwent impedance plethysmography at entry into the study so that subsequent impedance plethysmograms could be compared with that obtained at base line. The patients were assessed monthly for three months after randomization. Each visit included a history taking, physical examination, and impedance plethysmography. All the patients were instructed to report to the clinic on an emergency basis if any symptoms developed that were suggestive of deep-vein thrombosis or pulmonary embolism.

The principal outcome events studied in this trial were symptomatic recurrent venous thromboembolism within 90 days after randomization and bleeding during the period of administration of study medication or within 48 hours after its discontinuation.

Patients with symptoms or signs of recurrent deep-vein thrombosis underwent objective testing by impedance plethysmography, duplex ultrasonography, venography, or a combination of these techniques.^{11,12} Recurrent deep-vein thrombosis was diagnosed if there was a constant defect of intraluminal filling on venography or if there was a lack of compressibility on duplex ultrasonography and this finding represented a change from the results of tests of the deep-vein thrombosis qualifying the patient for the study. If the results of both venography and duplex scanning were inconclusive, recurrent deep-vein thrombosis was diagnosed if the impedance plethysmogram changed from normal to abnormal. Patients with clinically suspected pulmonary embolism underwent ventilation-perfusion lung scanning, and pulmonary embolism was diagnosed if the scan was considered to indicate a high probability of pulmonary embolism or a pulmonary angiogram was positive in a patient whose lung scan did not indicate such a probability.¹³

Bleeding was defined as major if it was overt and associated with either a decrease in the hemoglobin level of at least 2.0 g per deciliter or a need for the transfusion of 2 or more units of blood, or if it was retroperitoneal or intracranial.¹⁴ Bleeding was defined as minor if it was overt but did not meet the other criteria for major bleeding.

All reported outcome events were reviewed by a central adjudication committee whose members were unaware of the treatment assignments.

Statistical Analysis

On the basis of comparisons of low-molecular-weight heparin with standard heparin as in-hospital treatment,^{4,6} we assumed that low-molecular-weight heparin would be better than standard heparin—that is, that there would be a 3 percent rate of recurrent venous thromboembolism during the first three months of follow-up, as compared with a 6 percent rate with standard heparin. Under this assumption, and with the recruitment of 500 patients, there was a 94 percent probability (power) of rejecting, at the 5 percent level, the hypothesis that the rate of recurrence with low-molecular-weight heparin would be 3 percent higher than that with standard heparin.

The rates of recurrent venous thromboembolism, bleeding, and death in the two treatment groups were compared by Fisher's exact test. Ninety-five percent confidence intervals were calculated by the method of Thomas and Gart.¹⁵

RESULTS

Study Population

The recruitment of patients for the trial began in May 1992 and was completed in January 1995. During this period, we screened 2230 consecutive patients with acute proximal deep-vein thrombosis. Of these, 1491 were excluded for one or more of the following reasons: inability to receive outpatient therapy with low-molecular-weight heparin because of associated coexisting conditions (610 patients), concurrent symptomatic pulmonary embolism (229), previous treatment with standard heparin for more than 48 hours (137), geographic inaccessibility (116), two or more previous episodes of deep-vein thrombosis or pulmonary embolism (110), and other causes (289).

The remaining 739 patients were invited to participate in the trial, and 500 (68 percent) gave informed consent. Among those who did not give consent, the reasons for declining to participate were a desire to be admitted to the hospital (128 patients), a desire to receive standard heparin (43), an unwillingness to give themselves injections (38), a desire not to be admitted to the hospital (7), and other reasons (23).

Of the 500 patients who consented to participate in the study, 247 were randomly assigned to treatment with low-molecular-weight heparin and 253 were assigned to receive standard heparin. No patient was lost to follow-up. The base-line characteristics of the treatment groups were reasonably similar (Table 1).

Anticoagulant Therapy

The mean (\pm SD) duration of study treatment was 5.8 ± 1.8 days in the low-molecular-weight-heparin group and 5.5 ± 1.2 days in the standard-heparin group. In the low-molecular-weight-heparin group, 120 patients were not hospitalized at all, and 29 were admitted to the hospital to begin treatment with low-molecular-weight heparin. Of the remaining patients in that group, 76 were admitted to the hospital at night or on a weekend before randomization, and 22 had been hospitalized for other reasons, with deep-vein thrombosis developing during hospitalization. In the standard-heparin group,

Table 1. Base-Line Characteristics of the Study Patients.

CHARACTERISTIC*	LOW-MOLECULAR-WEIGHT HEPARIN (N = 247)	STANDARD HEPARIN (N = 253)
Mean (\pm SD) age (yr)	57 \pm 17	59 \pm 15
	<i>no. of patients</i>	
Male sex	153	148
History of DVT or pulmonary embolism	51	36
Recent surgery	52	45
Active cancer	46	57
Recent trauma	19	27
Method used to diagnose DVT		
Venography	91	100
Ultrasonography	156	153
Patient's category at presentation		
Outpatient	149	151
Patient hospitalized for DVT before randomization	76	81
Patient whose DVT developed during hospitalization for another reason	22	21

*DVT denotes deep-vein thrombosis.

2 patients refused admission to the hospital and received standard heparin subcutaneously at home with the dose adjusted according to the activated partial-thromboplastin time, 149 were randomly assigned to enter the hospital and receive standard heparin, 81 were admitted at night or on a weekend before randomization, and 21 were hospitalized for other reasons, with deep-vein thrombosis developing in the hospital. Among the patients who received standard heparin before randomization, this treatment lasted 22 ± 12 hours in the low-molecular-weight-heparin group and 21 ± 11 hours in the standard-heparin group.

When patients who had outcome events were excluded, 95 percent of patients assigned to low-molecular-weight heparin and 97 percent of those assigned to standard heparin received at least 11 weeks of oral anticoagulant therapy. The international normalized ratio was in the therapeutic range (between 2.0 and 3.0) 63 percent of the time in the low-molecular-weight-heparin group and 62 percent of the time in the standard-heparin group; it was below the range 19 and 21 percent of the time, respectively, and above the range 18 and 17 percent of the time.

Thromboembolism

During the 90 days after randomization, 13 patients assigned to receive low-molecular-weight heparin (5.3 percent) had symptomatic recurrent thromboembolism, as compared with 17 patients assigned to receive standard heparin (6.7 percent, $P=0.57$) (Table 2). Thus, there was an absolute difference of 1.4 percentage points in favor of low-molecular-weight heparin (95 percent confidence interval, -3.0 to 5.7). Two patients in the standard-heparin group had pulmonary embolism (on the day of randomization and day 6), and both died. In the low-molecular-weight-heparin group, 7 recurrences were observed in the first month after randomization, 4 in the second month, and 2 in the third month, as compared

with 12, 5, and no recurrences in the standard-heparin group in the respective months.

Complications Involving Bleeding

Major hemorrhagic complications occurred during the period of study-drug administration or the subsequent 48 hours in five patients assigned to receive low-molecular-weight heparin (2.0 percent) as compared with three patients assigned to receive standard heparin (1.2 percent, $P=0.50$) (Table 3). Two episodes of bleeding in the low-molecular-weight-heparin group were fatal; one patient had a subdural hematoma after a fall, and the other, who had associated thrombocytopenia due to chemotherapy and radiation, bled from an esophageal cancer. There were six episodes of minor bleeding in each group.

Five patients assigned to receive low-molecular-weight heparin and three patients assigned to receive standard heparin had platelet counts below 100,000 per cubic millimeter during the period of study-drug administration; for one patient in each group, there was no apparent explanation for the low platelet count.

Mortality

During the 90-day study period, 11 patients receiving low-molecular-weight heparin died, as compared with 17 patients receiving standard heparin.

Hospital Stay

After randomization, the mean time spent in the hospital by the patients assigned to low-molecular-weight heparin was 1.1 ± 2.9 days, as compared with 6.5 ± 3.4 days by the patients assigned to standard heparin (Table 4). Among the 247 patients assigned to low-molecular-weight heparin, 120 were never admitted to the hospital, and the remaining 127 spent an average of 2.2 ± 3.8 days in the hospital after randomization.

DISCUSSION

Patients with proximal deep-vein thrombosis generally require hospitalization in order to receive standard heparin by continuous intravenous infusion. Our study shows that enoxaparin, a low-molecular-weight heparin, can be used safely and effectively to treat patients at home who have this condition. The rates of recurrent

Table 3. Episodes of Major Bleeding in Eight Patients during the Study.

TREATMENT GROUP AND EVENT	STUDY DAY	INR*	ACTIVATED PARTIAL-THROMBOPLASTIN TIME (SEC)
Low-molecular-weight heparin (n = 5)			
Soft-tissue hematoma of hip	6	2.7	27
Abdominal-wall hematoma	7	2.7	55
Abdominal-wall hematoma	7	3.2	40
Subdural hematoma†	5	3.4	40
Hematemesis‡	6	2.4	40
Standard heparin (n = 3)			
Hematuria	2	1.3	64
Gastrointestinal bleeding	3	3.0	88
Hematemesis	1	2.7	64

*INR denotes international normalized ratio.

†The patient died as a result of this episode of bleeding.

‡The patient had cancer and associated thrombocytopenia due to chemotherapy and radiation.

thromboembolism and major bleeding in both treatment groups were low and did not differ significantly between treatment groups. The 95 percent confidence interval for the absolute difference between rates of thrombosis indicated that outpatient therapy with enoxaparin was unlikely to be more than 3 percent worse than treatment with standard heparin. The results of our randomized trial are consistent with the findings of previous studies demonstrating that preparations of low-molecular-weight heparin are at least as effective and safe as standard heparin in the initial treatment of hospitalized patients with deep-vein thrombosis.⁴⁻⁶

In one study⁵ and a meta-analysis¹⁶ in which the two treatments were compared, there were statistically significant reductions in mortality in favor of low-molecular-weight heparin. In our study, there was a nonsignificant trend in favor of low-molecular-weight heparin.

Treating patients with acute proximal deep-vein thrombosis requires the use of heparin at first, combined with at least three months of warfarin therapy.^{17,18} In the early trials comparing standard heparin with low-molecular-weight heparin in hospitalized patients, venography was performed at entry into the study and approximately one week later.^{3,19,20} The primary outcome measure in these trials was a change in the size of the thrombus, a surrogate for clinically recurrent thrombosis. The primary outcome measure in the more recent larger trials in hospitalized patients was symptomatic recurrent venous thromboembolism.^{4,5} This measure was also used in our trial. We did not routinely screen our patients by ultrasonography or venography at specified times, and thus silent recurrences may have gone undetected.

This was not a double-blind study, but we took special care to minimize bias in the assessment of recurrent venous thrombosis and bleeding. Patients were instructed to report to the study team without waiting to make a scheduled visit if any symptoms compatible with recurrent deep-vein thrombosis or pulmonary embolism developed. All suspected recurrences were evaluated by objective tests, and all outcome events

Table 2. Recurrences of Thromboembolism during the Study.

EMBOLIC EVENT	LOW-MOLECULAR-WEIGHT HEPARIN (N = 247)	STANDARD HEPARIN (N = 253)
	no. of patients (%)	
Deep-vein thrombosis	11	15
Pulmonary embolism	1	2*
Both	1	0
All cases	13 (5.3)	17 (6.7)

*These two patients died during the study.

Table 4. Mean (\pm SD) Hospital Stays of the Study Patients after Randomization, According to Treatment Group and Category of Patient.

CATEGORY OF PATIENT	LOW-MOLECULAR-WEIGHT HEPARIN		STANDARD HEPARIN	
	NO. OF PATIENTS	NO. OF DAYS	NO. OF PATIENTS	NO. OF DAYS
Outpatient	149*	0.9 \pm 2.3	151†	6.7 \pm 3.4
Patient hospitalized for deep-vein thrombosis before randomization	76	1.0 \pm 1.8	81	6.2 \pm 3.8
Patient whose deep-vein thrombosis developed during hospitalization for another reason	22	3.0 \pm 6.8	21	6.4 \pm 1.9
All	247	1.1 \pm 2.9	253	6.5 \pm 3.4

*Of these outpatients, 120 were not admitted to the hospital at all.

†Two of these patients were not admitted to the hospital but received subcutaneous standard heparin at home.

were evaluated by a committee unaware of the treatment assignments.

Of the 2230 patients with acute proximal deep-vein thrombosis whom we screened, 739 (33 percent) met the study criteria requiring eligibility for either immediate outpatient treatment or early discharge from the hospital. Given some of the reasons for exclusion (e.g., geographic inaccessibility), the actual proportion of patients to which the study findings are applicable may be somewhat higher.

Of the 247 patients randomly assigned to receive low-molecular-weight heparin, 120 were never admitted to the hospital, and the remaining 127 patients spent an average of 2.2 days in the hospital after randomization. The average hospital stay for all patients in this group was 1.1 days, as compared with 6.5 days for the patients receiving standard heparin. We included the patients who were discharged early in the study in order to extend the potential convenience and cost savings associated with out-of-hospital treatment with low-molecular-weight heparin to a broader population.

Two other randomized studies^{21,22} have also evaluated the home administration of low-molecular-weight heparin in the long-term treatment of patients with deep-vein thrombosis. In both studies, patients were first treated in the hospital with standard heparin, and then therapy with low-molecular-weight heparin was compared with therapy for three to six months with warfarin²¹ or subcutaneous standard heparin.²²

Low-molecular-weight heparins share a number of properties, but they differ in profiles of the distribution of molecular weight, specific activities (measured as the ratio of factor Xa to factor IIa), rates of clearance from plasma, and recommended dosage regimens.³ It should not be assumed that all low-molecular-weight heparins have similar benefits. In conclusion, our study indicates that many patients with acute proximal deep-vein thrombosis can be treated safely and effectively at home with subcutaneous enoxaparin at doses adjusted for the patient's weight, increasing the convenience for the patient and reducing the cost to the health care system substantially.

APPENDIX

The following institutions, all in Canada, participated in this study. Hamilton Civic Hospitals, Hamilton, Ont.; Chedoke-McMaster Hospitals, Hamilton, Ont.; St. Joseph's Hospital, Hamilton, Ont.; Sunnybrook Health Science Centre, Toronto; Victoria Hospital, London, Ont.; University Hospital, London, Ont.; St. Joseph's Hospital, London, Ont.; Montreal General Hospital, Montreal; Maisonneuve-Rosemont Hospital, Montreal; Hôtel-Dieu de Montréal, Montreal; St.-Sacrement Hospital, Quebec, Que.; Centre Hospitalier de l'Université Laval, Quebec, Que.; Victoria General Hospital, Halifax, N.S.; St. Paul's Hospital, Vancouver, B.C. (J. Ward); and Health Sciences Centre, St. John's, Newf. (C. Whitman).

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