Abbreviated Hospitalization for Deep Venous Thrombosis With the Use of Ardeparin

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Background: Ardeparin sodium has recently received approval by the Food and Drug Administration for prophylaxis against venous thromboembolism in patients undergoing elective total knee replacement. However, this low-molecular-weight heparin has not been previously evaluated in a randomized controlled trial for treatment of established acute deep venous thrombosis.

Methods: The study included patients with ultrasound-documented acute symptomatic deep venous thrombosis of the legs. They had to be deemed appropriate for discharge home to receive subcutaneous low-molecular-weight heparin. Patients were randomized to receive ardeparin with a 2-day hospitalization or unfractionated heparin sodium with a 5-day hospitalization. Both groups received warfarin sodium. Follow-up ultrasound examinations were undertaken at 6 weeks.

Results: Of the 80 patients enrolled, 75 had follow-up ultrasonography. Evaluation of baseline vs 6-week venous scans demonstrated that, overall, 31 of the 39 ardeparin-treated patients improved, compared with 21 of the 36 patients assigned to receive unfractionated heparin (P = .05). The 95% confidence interval for the difference in improvement was 0.6% to 42% in favor of ardeparin. Median charges for ardeparin and unfractionated heparin were $2815 and $6500, respectively (P < .001). There were no differences in bleeding or patient satisfaction between the 2 groups.

Conclusions: The results of this small preliminary trial suggest that ardeparin can be administered effectively and safely to selected patients with acute deep venous thrombosis and that, with proper nursing and home services, it can help decrease the duration of hospitalization.

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Ardeparin sodium has recently received approval by the Food and Drug Administration for prophylaxis against venous thromboembolism in patients undergoing elective total knee replacement. However, this low-molecular-weight heparin has not been previously evaluated in a randomized controlled trial for treatment of established acute deep venous thrombosis (DVT). Therefore, in a single-center, investigator-initiated trial, we tested the feasibility of using a shortened hospital stay with ardeparin to treat symptomatic patients with acute DVT proved on ultrasound. They were randomized to receive either twice-daily subcutaneously injected ardeparin with a 2-day hospitalization or conventional continuous-infusion unfractionated heparin sodium with a 5-day hospitalization as a bridge to oral anticoagulation with warfarin sodium. In this feasibility study, we assessed efficacy, safety, hospital charges, and patient satisfaction in the 2 treatment groups.

RESULTS

Overall, 80 patients were randomized, 41 to receive ardeparin and 39 to receive unfractionated heparin. Baseline characteristics were similar in both groups (Table 1). Of the 80 patients, there were no deaths or recurrent DVTs. There was 1 symptomatic, hemodynamically stable pulmonary embolism diagnosed by moderately high-probability lung scan in a patient assigned to receive unfractionated heparin. Adverse clinical events are shown in Table 2. One patient in each group suffered a major bleeding complication. The patient assigned to the unfractionated heparin group had an intraocular hemorrhage, and the patient who received ardeparin had undergone thoracic surgery and developed mediastinal bleeding.
PATIENTS AND METHODS

PATIENTS

The study included patients 18 years of age or older who had acute (within 14 days) symptomatic DVT of the legs. They had to be deemed appropriate for discharge home to receive subcutaneous low-molecular-weight heparin, and DVT had to be documented by ultrasound. Our Human Research Committee approved this trial, and each patient provided written informed consent.

Principal exclusion criteria were high-risk DVT involving 3 proximal veins (eg, common femoral, superficial femoral, and popliteal veins); pelvic vein thrombosis; involving 3 proximal veins (eg, common femoral, superficial femoral, and popliteal veins); pelvic vein thrombosis; current symptomatic pulmonary embolism; expected prolonged hospitalization for other reasons; hemoglobin level less than 85 g/L or platelet count less than 100,000/μL; intracranial or intracranial surgery, stroke, or internal bleeding within 3 months; or weight of 120 kg or more.

Randomization was accomplished by calling a central computerized service based at Wyeth-Ayerst Research, Philadelphia, Pa. The drug assignment was not blinded.

METHODS

Patients assigned to the ardeparin sodium group received 130 anti-Xa U/kg subcutaneously twice daily and were hospitalized for 36 to 48 hours. Ardeparin was administered (usually by the patient) for 3 to 15 days, while warfarin sodium, 7.5 to 10 mg, was initiated and titrated to a therapeutic and stable international normalized ratio of 2.0 to 3.0. During ardeparin treatment, daily international normalized ratios were obtained and, after discharge, a study nurse (R.B.M.) telephoned the patient daily to discuss warfarin dosing as well as overall progress. Patients assigned to the unfractionated heparin sodium group received a 5000- to 7500-unit bolus followed by a continuous intravenous infusion administered for 5 days or more to achieve a target partial thromboplastin time of 1.5 to 2.5 times the upper limit of the control. Titration of unfractionated heparin was guided by the Cruickshank et al nomogram and was discontinued after 5 days as long as the target international normalized ratio had been achieved.

Hospital charges were tracked and computed by the Computer Assisted Hospitalization Analysis for the Study of Efficacy at Brigham and Women's Hospital, Boston, Mass. These consisted of charges for room, board, laboratory tests, medications, and imaging tests. All patients were discharged home with vascular compression stockings and were scheduled to return for 2-week and 6-week office visits. We instructed all patients about signs and symptoms of recurrent venous thromboembolism. We provided them with 24-hour emergency telephone numbers. We also suggested to patients in the ardeparin group that they not return to their usual activity level until ardeparin was discontinued.

The principal efficacy end point was the change on the 6-week ultrasound scan compared with baseline (Table 3). Fifteen ardeparin-treated patients compared with 8 patients who received unfractionated heparin had previous venous thromboembolism (P < .001). Overall, 31 (79%) of the 39 ardeparin-treated patients improved, compared with 21 (58%) of the 36 patients assigned to the unfractionated heparin group (P = .05). The 95% confidence interval for the difference in improvement was 0.6% to 42% in favor of ardeparin.

Patients were given a satisfaction questionnaire to return at the time of their 2-week visit. At the 6-week office visit, they underwent venous ultrasonography. During the time from hospital discharge to 6 weeks, international normalized ratios were checked at least once weekly. At the 6-week visit, the trial ended and management of warfarin dosing was transferred to the primary care physician.

A sonographic unit (Acuson 128; Acuson, Mountain View, Calif) was used to perform venous ultrasound examinations of the lower extremities, with the use of 3- and 7-MHz transducers (duplex and color pulsed Doppler capacity). Studies were obtained at baseline (before treatment) and were repeated at 6 weeks.

Examinations were performed by compressing the deep veins of the thigh and the calf in a sequential manner in 1- to 2-cm increments along the common femoral, superficial femoral, popliteal, posterior tibial, peroneal, gastrocnemius, and soleus veins. Lack of venous compressibility with the ultrasound transducer held transverse to the artery and vein was interpreted as an abnormal study result and was confirmed with color-flow and pulsed-wave Doppler analysis. Absent or diminished Doppler flow, lack of respiratory variation, and failure to augment flow with maneuvers (calf compression) were used to confirm the diagnosis of DVT. One of us (M.A.C.) was responsible for adjudicating the comparison of baseline and 6-week follow-up ultrasound scans. He had no knowledge of the randomization assignment. Improvement, no change, and worsening of DVT were defined by regression, no change, or extension, respectively, of visualized thrombus.

We previously found that duplex ultrasonography, when compared with venography, is a reliable technique for the detection of suspected infrapopliteal DVT. In a series of 30 symptomatic patients undergoing both contrast venography of the calf veins and ultrasonography, 7 had venographically documented isolated calf DVT, and all 7 cases were detected by ultrasonography.

STATISTICAL ANALYSIS

Data were entered into TRUE EPISTAT files and analyzed by means of TRUE EPISTAT software (Epistat Services, Richardson, Tex). Student t test was used to examine differences among continuous variables with normal distributions. The Wilcoxon rank sum test was used when continuous variables failed tests for normality. Differences among discontinuous variables were analyzed with Epi Info software (version 5.01b; Centers for Disease Control and Prevention, Epidemiology Program Office, Atlanta, Ga) by means of χ² with the Yates correction, except with expected cell values less than 5, in which case Fisher exact 2-tailed test was used. Confidence intervals were calculated with the use of confidence interval analysis software (Confidence Interval Analysis, version 1.0; British Medical Journal, London, England).
talization, compared with the ardeparin group, which averaged 2.2 days of hospitalization (Table 4). For example, the median charges were $6500 and $2815, respectively (Figure).

According to a patient satisfaction scoring system in which 1 indicates excellent; 2, very good; 3, good; 4, fair; and 5, poor, both groups reported an average score of 1.3 for the care that they received. At 2 weeks, there was no difference between ardeparin and unfractionated heparin treatment with respect to activities of daily living. Regarding length of stay, 5 ardeparin-treated patients thought their hospital stay was “a little shorter than needed,” whereas 6 patients treated with unfractionated heparin thought their hospital stay was “a little longer than needed” (Table 5).

This trial demonstrates the probability that among a relatively small group of properly selected patients with DVT, ardeparin administration can be used in lieu of unfractionated heparin to shorten the hospitalization period and decrease hospital charges. Efficacy, in terms of thrombus resolution, was greater with ardeparin than with un-
fractionated heparin, and safety and patient satisfaction were similar with ardeparin and unfractionated heparin. The principal difference between the 2 management strategies in these groups was the dramatically decreased hospital charges among ardeparin-treated patients. It is important to note that the dose of ardeparin sodium, 130 anti-Xa U/kg, far exceeds the dose of 50 anti-Xa U/kg recently approved for DVT prophylaxis among patients undergoing total knee replacement.

Other low-molecular-weight heparins have been demonstrated to be effective in the management of DVT. These include reviparin sodium, enoxaparin sodium, nadroparin calcium, tinzaparin sodium, and dalteparin sodium. Enoxaparin and nadroparin were specifically used to test the strategy of an abbreviated hospitalization or, in some instances, completely outpatient DVT management. However, each low-molecular-weight heparin has special biochemical characteristics. For example, ardeparin is prepared by peroxidative depolymerization; it has an average molecular weight of 6000 daltons and an anti-Xa to anti-IIa ratio of 2.0. In contrast, enoxaparin is prepared by benzylation and alkaline depolymerization. It has an average molecular weight of 4200 daltons and an anti-Xa to anti-IIa ratio of 3.8.

This study is limited by small sample size. To plan this trial with the goal of 95% confidence and 80% power to detect a 20% improvement in efficacy among ardeparin-treated patients, based on the observed 58% improvement rate in the unfractionated heparin group, a sample size of about 400 patients would have been required.

The present study extends the beneficial results of ardeparin for orthopedic surgical prophylaxis to the treatment of established acute DVT. In a dose more than 2.5 times greater than that used for prophylaxis, ardeparin was demonstrated to be more effective and as safe as unfractionated heparin. The use of ardeparin permitted implementation of an early discharge strategy, which conserved the resources associated with 3 incremental days of hospitalization per patient. Importantly, this strategy was instituted without a decrement in overall patient satisfaction. In summary, this trial suggests that ardeparin can be administered effectively and safely to selected patients with acute DVT. With proper nursing and home services, it can be used to help decrease the duration of hospitalization. However, a larger and more definitive study should be undertaken to confirm our findings.

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REFERENCES