Abbreviated Hospitalization for Deep Venous Thrombosis With the Use of Ardeparin

Samuel Z. Goldhaber, MD; Ruth B. Morrison, RN, BSN, CVN; Linda L. Diran, BS; Mark A. Creager, MD; Thomas H. Lee, Jr, MD

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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Aerdeparin 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.

From the Cardiovascular Division, Department of Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston, Mass.

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Overall, 31 (79%) of the 39 ardeparin-treated patients had previous venous thromboembolism (P < .001) compared with 8 patients who received unfractionated heparin. 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.

Hospital charges were greater in the unfractionated heparin group, which averaged 5.7 days of hospitalization compared to 3.0 days (P = .001). Five (13%) of the 39 ardeparin-treated patients had intracranial or intraocular surgery, stroke, or internal bleeding during ardeparin treatment. During ardeparin treatment, daily international normalized ratios were obtained and 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.

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 $\chi^2$ with the Yates correction, except with expected cell values less than 5, in which case Fischer 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 4000 daltons and an anti-Xa to anti-IIa ratio of 2.0. In contrast, enoxaparin is prepared by benzylaion 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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Reprints: Samuel Z. Goldhaber, MD, Cardiovascular Division, Brigham and Women's Hospital, 75 Francis St, Boston, MA 02115 (e-mail: szgoldhabe@bics.bwh.harvard.edu).

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