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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Overall, 31 (79%) of the 39 ardeparin-treated patients im-
rinin had previous venous thromboembolism (the 6-week ultrasound scan compared with baseline
(Table 3)

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. Dur-
ing the time from hospital discharge to 6 weeks, interna-
tional normalized ratios were checked at least once
weekly. At the 6-week visit, the trial ended and manage-
ment 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 ex-
aminations of the lower extremities, with the use of 3- and
7-MHz transducers (duplex and color pulsed Doppler ca-
pacity). Studies were obtained at baseline (before treat-
ment) 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 fem-
oral, superficial femoral, popliteal, posterior tibial, pero-
neal, gastrocnemius, and soleus veins. Lack of venous
compressibility with the ultrasound transducer held
verse 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 (call compression) were
used to confirm the diagnosis of DVT. One of us (M.A.C.)
was responsible for adjudicating the comparison of base-
line and 6-week follow-up ultrasound scans. He had no
knowledge of the randomization assignment. Improve-
ment, no change, and worsening of DVT were defined by
regression, no change, or extension, respectively, of visu-
ized 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, Ri-
charstown, Tex). Student t-test was used to examine differ-
ences among continuous variables with normal distribu-
tions. The Wilcoxon rank sum test was used when
continuous variables failed tests for normality. Diff-
erences among discontinuous variables were analyzed with
Epi Info software (version 5.01b; Centers for Disease Con-
trol and Prevention, Epidemiology Program Office, At-
tanta, Ga) by means of χ² with the Yates correction,
cept 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 analy-
sis software (Confidence Inteviev Analysis, version 1.0;

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

Hospital charges were greater in the unfraction-
ated heparin group, which averaged 5.7 days of hospi-
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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