A Pilot Study of Home Treatment of Deep Vein Thrombosis With Subcutaneous Once-Daily Enoxaparin Plus Warfarin

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ABSTRACT

OBJECTIVE: To evaluate patient satisfaction, effectiveness, and safety of at-home treatment of acute deep vein thrombosis (DVT) with subcutaneous enoxaparin dosed at 1.5 mg/kg once daily plus oral warfarin.

METHODS: Patients with acute DVT and no more than 1 previous episode of DVT received enoxaparin plus oral warfarin until their international normalized ratio (INR) was >2 on 2 consecutive days. Patients were recruited between November 2000 and June 2003, and a home-care nurse visited the patient daily to administer the enoxaparin and to perform a fingerstick INR test. Patients received warfarin at doses adjusted to maintain an INR in the range of 2 to 3. Efficacy and safety were assessed daily by a home-care nurse and then by telephone interview conducted by a pharmacist at 14, 30, and 90 days during follow-up. Patient satisfaction with treatment was assessed by a verbal questionnaire.

RESULTS: There were 52 patients enrolled. The mean duration of enoxaparin home treatment was 4.5 days, and the mean INR on discontinuation of enoxaparin was 2.73. Most patients (84.6%) had INRs within the desired therapeutic range (INR value 2-3); no patient had a subtherapeutic INR. There were no symptoms of recurrent venous thromboembolism reported. Major bleeding occurred 7 days after discontinuation of enoxaparin in one patient with impending surgery for removal of a uterine tumor. There were 2 cases of minor bleeding. The patient satisfaction questionnaire revealed that patients considered home treatment to be acceptable. The average cost savings was \$2,925 per patient compared with typical inpatient treatment with unfractionated heparin.

CONCLUSION: The results of this pilot study suggest that home treatment with initial once-daily enoxaparin in conjunction with long-term oral warfarin is a safe and effective alternative to inpatient therapy with once-daily enoxaparin or unfractionated heparin for select patients with acute DVT. Cost savings are derived from the substitution of inpatient care with home care.

KEYWORDS: Outpatients, Home treatment, Enoxaparin, Deep vein thrombosis, Thromboembolism

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Deep vein thrombosis (DVT) affects approximately 1 of every 2,000 people in the general population each year in the United States^{1,2} and is a major cause of mortality and morbidity because of the risk of complications such as pulmonary embolism (PE) and postthrombotic syndrome. The economic costs and the inconvenience to the patient of in-hospital treatment of DVT create a strong rationale for safe and effective home anticoagulant therapy in eligible patients.

Traditionally, the treatment of DVT involved unfractionated heparin (UFH) administered intravenously in a hospital setting for 5 to 7 days.³ However, the use of UFH requires hospitalization for close monitoring because of the narrow therapeutic index and a nonlinear dose-response relationship that shows marked variation between individuals.^{3,4} By contrast, low-molecular-weight heparins (LMWHs) offer a more predictable pharmacokinetic profile and anticoagulant effect and can be administered by subcutaneous injection without routine anticoagulation monitoring.⁵ Several studies have shown that LMWHs are at least as effective as intravenous (IV) UFH in the in-hospital treatment of DVT.⁶⁻⁸ Furthermore, the ability to administer LMWHs subcutaneously makes it feasible to treat patients in their home, rather than in the hospital. Although treatment in an outpatient setting offers the benefits of convenience for the patient and the potential to reduce hospital costs,⁹⁻¹³ many physicians may be reluctant to use this approach, possibly because of a belief that the controlled conditions of clinical trials are not representative of the real-world clinical situation. While large randomized trials have shown that twice-daily LMWH treatment at home is effective and well tolerated compared with UFH treatment in the hospital,¹⁴⁻¹⁶ less data are available to support once-daily dosage of enoxaparin on an outpatient basis.^{17,18}

We carried out a pilot study in patients with acute DVT to evaluate the convenience, efficacy, and safety of the LMWH enoxaparin, 1.5 mg/kg, given once daily in a real-world U.S. patient population eligible for home treatment.

Methods

The study was a prospective, nonrandomized, open-label study performed at a single center in the United States enrolling patients eligible for home care with LMWH. William Beaumont Hospital is a 1,085-bed community, nonprofit, teaching hospital located in Royal Oak, Michigan. The study was conducted according to the Declaration of Helsinki and approved by the hospital's Institutional Review Board. Written informed consent was obtained from all patients before inclusion in the study.

Patients were enrolled between November 2000 and June 2003. Adult patients with acute proximal DVT confirmed by Doppler ultrasound were eligible for the study if they met the eligibility criteria for home therapy summarized in Table 1. Patients were recruited from the emergency room, a short-stay ambulatory unit, and inpatient areas of the hospital. Baseline laboratory assessment included serum creatinine, hemoglobin, platelets, and prothrombin time. On the day of hospital discharge, all patients were administered a single subcutaneous (SC, 1.5 mg/kg) dose of enoxaparin (Lovenox). Prior to discharge, patients were provided with a 7-day supply of enoxaparin and 25 tablets of 2.5 mg warfarin (Coumadin). Patients or their caregivers were educated by a pharmacist prior to discharge and by the home care nurse at the first visit. Education included the purpose of anticoagulant therapy, anticoagulant monitoring, and signs and symptoms of adverse events, with a signed educational checklist added to the inclusion criteria to ensure that each patient was fully informed.

Initially, patients received enoxaparin 1.5 mg/kg SC once daily, administered by a home-care nurse, and daily oral warfarin dosage titrated by a pharmacist. The international normalized ratio (INR) was monitored every 1 to 3 days by fingerstick testing (CoaguChek, Roche Diagnostics), and the warfarin dose was adjusted until the target range (2-3) was recorded for 2 consecutive days. Daily nursing visits ceased when a second INR was verified to be in the therapeutic range (with no enoxaparin administered on the final day of home nursing visits). Warfarin treatment was then continued with INR monitoring done by venous draw (not fingerstick) and dose adjustment was at the discretion of the patient's private physician and not recorded for the study. Adherence to warfarin therapy was confirmed by telephone follow-up at 14, 30, and 90 days. To document cases of readmission, hospital computer records were checked and patients were questioned at the follow-up intervals to ensure that readmission to another institution would be reported.

Efficacy and safety were assessed daily during enoxaparin treatment and at 14, 30, and 90 days during follow-up warfarin therapy. Assessments were made by telephone interviews using a questionnaire to confirm the absence of signs or symptoms of thromboembolism (PE or DVT), bleeding, or other adverse events. Efficacy outcome was the absence of repeat thromboembolic symptoms. For example, patients were asked whether the lower limb pain or swelling had changed (which could indicate worsening of the DVT) or if they had experienced any shortness of breath or chest pain (which could indicate progression of DVT to PE). Safety outcomes were signs or symptoms of any adverse events, including bleeding, allergy, or death. For example, patients were asked whether they had any nosebleeds, bruising, rashes, or blood in stools, urine, or the mouth. A major bleed was defined as a drop in hemoglobin of >2 g/dL or evidence of any intracranial bleed or retroperitoneal bleed.

TABLE 1 Inclusion and Exclusion Criteria for Outpatient Treatment of DVT

Inclusion criteria:

- Age ≥ 18 years
- Diagnosis of DVT confirmed by ultrasound
- Are medically stable and otherwise ready for discharge
- Suitable home environment with supportive care and phone
- Ability to understand and sign consent form and educational assessment*

Exclusion criteria (excluded: n=128)

- Other bleeding and/or hematological disorders (e.g., coagulopathy; hemoglobin <11 g/dL in men or <9 g/dL in women; platelets <100 cells/mm³) [44]†
- Renal failure (e.g., creatinine clearance <30 mL/min) [32]
- ≥ 2 previous episodes of DVT [22]
- Surgery in last 2 weeks [13]
- Acute PE or clot with ileo-caval involvement [9]
- Total body weight >150% of lean body weight [5]
- Pregnancy [2]
- Concurrent epidural analgesia [1]
- Recent history of bleeding, PE, or peptic ulcer in last 2 weeks [0]
- Hypertension (e.g., >180 mm Hg systolic or >110 mm Hg diastolic blood pressure over 24 hours) [0]
- Heparin-associated antibody [0]

* An educational checklist was signed by the patient or caregiver to ensure that there was adequate education provided regarding the purpose of anticoagulant therapy, anticoagulant monitoring, and signs and symptoms of adverse events.

† Numbers in brackets after criteria indicate the number of patients excluded because of that criteria.

DVT=deep vein thrombosis; PE=pulmonary embolism.

TABLE 2 Baseline Patient Characteristics (n = 52)

Characteristic	Number (%)
Enrolled as inpatients started on UFH	32
Enrolled directly from emergency room	20
Age, years ($\pm$ SD)	58 ($\pm$ 14.2)
Weight, kg ($\pm$ SD)	88.3 ($\pm$ 18.3)
Male, n (%)	38 (73.1)
Receiving concomitant therapy:	
Aspirin	8 (15.4)
Clopidogrel	1 (1.9)
Ibuprofen	2 (3.8)
Allopurinol	2 (3.8)

UFH=unfractionated heparin.

A secondary outcome was the number of days required to reach the INR target.

Patient satisfaction with treatment was assessed during follow-up by means of a questionnaire consisting of 3 questions:

1. Were you satisfied with the pain control?
2. Were you satisfied with the nursing visits?
3. Were you satisfied with the fingerstick INR blood test method?

TABLE 3 Efficacy and Safety Outcomes (n=52)

Finding	Number
Mean number of outpatient days to reach therapeutic INR ($\pm$ SD)	4.5 ($\pm$ 2.1) (range, 1-12 days)
Treatment duration (doses) ($\pm$ SD)	4.5 ($\pm$ 2.1)
Mean INR at LMWH discontinuation ($\pm$ SD)	2.73 $\pm$ 0.74
Patients at therapeutic INR at LMWH discontinuation (%)	44 (84.6%)
Patients at supratherapeutic INR (>3) at LMWH discontinuation (%)	8 (15.4%)
Patients with major bleeding (%)	1 (1.9%)*
Patients with minor bleeding (%)	2 (3.8%)

* One patient was lost to follow-up, withdrawn from study at day 13 because of impending surgery.

INR=international normalized ratio (therapeutic INR=2.0 to 3.0);
LMWH=low-molecular-weight heparin.

TABLE 4 Cost Analysis

Therapy	Costs (\$)
Outpatient DVT treatment daily costs:	
Medications (enoxaparin)*	85
Home nursing	118
Laboratory fees	30
Outpatient total cost per day	233
Inpatient DVT treatment daily costs:	
Medications (UFH)*	3
Inpatient bed cost and monitoring	880
Inpatient total cost per day	883
Medication costs for treatment duration†:	
UFH	14
Enoxaparin	383
Cost increase for pharmacy for enoxaparin vs. UFH	369
Total cost of therapy for treatment duration†:	
UFH in-hospital	3,974
Enoxaparin in-home	1,049
Cost saving of outpatient therapy	2,925

* Medication costs were based on average wholesale price during the study period; enoxaparin cost was based on average dose for the study group (120 mg).

† Duration of therapy was based on an average of 4.5 days to therapeutic international normalized ratio; billed charges for inpatient and home nursing visits were based on average annual rates during the study period (November 2000–September 2003), which ranged from an estimated \$700 to \$900 for inpatient room and board (estimate obtained from chief financial officer) and \$96 to \$126 per day for home nursing care visits over this nearly 4-year period.

DVT=deep vein thrombosis; UFH=unfractionated heparin.

Results

Of 233 patients screened for enrollment, 53 declined participation (through either the patient or primary care physician), and 128 were excluded by the exclusion criteria (Table 1). The reason(s) for ineligibility were: low hemoglobin or platelet count (44), creatinine clearance <30 mL/min (32), ≥ 2 DVT by history (22), recent surgery (13), PE or clot with ileo-caval involvement (9), total body weight greater than 150% of lean body weight (5), pregnancy (2), and spinal epidural (1). Patient demographics are shown in Table 2. A total of 52 patients were recruited, of whom 32 were inpatients started on UFH (average UFH treatment duration 3.25 ± 1.93 days), and 20 (38%) presented to the emergency room but were not subsequently admitted for inpatient care. Of the recruited patients, 51 completed the study; 1 patient was removed on physician advice due to hemorrhage at a uterine tumor site that resulted in surgery prior to further DVT treatment. For those patients receiving concomitant therapy with aspirin, clopidogrel, ibuprofen or allopurinol (n=13), none noted bleeding.

Efficacy and safety outcomes are summarized in Table 3. The mean duration of enoxaparin treatment was 4.5 days, equating to 4.5 doses of enoxaparin when allowing for the dose on discharge from hospital and no dose given on the final day of home-care visits. The mean INR at the time of enoxaparin discontinuation was 2.73; a total of 44 patients (84.6%) had INRs within the therapeutic range, and, of the remaining patients, all had supratherapeutic INRs (>3).

There were no reports of symptoms that could indicate recurrent DVT or PE during the study. Major bleeding, resulting in a 3.6-g/dL decrease in hemoglobin concentration, occurred in one patient (1.9%) who subsequently underwent removal of a uterine tumor on day 13 of warfarin treatment (7 days after discontinuation of enoxaparin). This patient was withdrawn from the study due to impending surgery. This patient was the only readmission to the hospital identified in the study. There were 2 (3.8%) cases of minor bleeding: at the injection site in one patient and scleral hemorrhage in the other patient.

The 3-item patient satisfaction questionnaire, for which there was a 100% response rate, revealed that patients considered home treatment to be convenient. All 52 patients reported that they were satisfied with their pain control and understood the methods to reduce leg pain (i.e., they verbalized that raising the leg or taking acetaminophen were sufficient measures for relief). The fingerstick method of blood monitoring (compared with conventional venous blood sampling) was satisfactory to all patients, and 22 patients (42%) expressed an interest in continuing this method, had it been made available, after the home-care nurse was discontinued because it was “less painful” and “less invasive” than the venous method. Forty-seven patients (90.4%) were satisfied with the home-care nursing visits.

Of the 45 patients for whom cost data were recorded (limited by availability of records in 7 cases), there were 4.3 daily home

Only descriptive statistics were used in this study.

For the same study period, billing and payment data for daily home nursing visits were recorded for enrolled patients. The patient or third-party payer was billed for the number of visits, and the payment was recorded.

visits at a billed charge per visit of $\$118 \pm 9.7$. The overall cost for home-care treatment was compared with the cost for typical inpatient UFH treatment over the same study period. The average savings were $\$2,925$ per patient despite higher pharmacy costs (Table 4). Average reimbursement for home nursing visits was 90% of billed charges ($\$457 \pm 187$).

Discussion

The results of this pilot study suggest that once-daily treatment with enoxaparin at a dose of 1.5 mg/kg, delivered at home in conjunction with long-term therapy with warfarin, is convenient, effective, and safe for the treatment of eligible patients with DVT. Patients considered at high risk were excluded from the present study. Compared with previous practice in this medical center, inpatient hospital days were either decreased or avoided. In the present study, there were no episodes of recurrent DVT symptoms, no symptoms of PE, and no serious adverse events related to enoxaparin. The one case of major bleeding occurred in a patient with a uterine tumor with impending surgery for its removal, and the bleeding was not considered related to enoxaparin.

These results are consistent with those of recent randomized comparative trials (Table 5) in which outpatient treatment with SC enoxaparin, either once or twice daily, was as effective as in-hospital treatment with IV UFH.^{14,17,18} This observational study adds to the accumulating evidence to support the use of outpatient enoxaparin once daily and is in accord with a recent position statement encouraging the development and documentation of outpatient DVT treatment programs.¹³

Once-daily administration offers obvious advantages over twice-daily treatment in terms of greater convenience for both patients and nursing staff. This greater convenience was reflected in the high levels of patient satisfaction reported in this study. Moreover, the reduced number of hospital visits required with once-daily treatment at home offers potential savings in the costs of nursing staff, drugs, and consumables.⁹⁻¹¹ Such savings are due largely to reductions in costs associated with hospitalization. In the present study, outpatient treatment of DVT with enoxaparin once daily provided 74% lower costs when compared retrospectively with typical inpatient UFH therapy for the same treatment duration (Table 4). The average saving of $\$2,925$ per patient was realized despite higher pharmacy costs.

A prior retrospective analysis of average length of stay in those patients receiving UFH at our hospital found that, for the period 1998-2000, 165 patients were hospitalized for an average 5.5 days (range, 3-9). Therefore, the savings in actual practice may be larger and will certainly be different in other medical centers. In addition, the actual payer costs may be higher or lower than our findings since reimbursement for home nursing visits in the present analysis was approximately 90% of billed charges.

Thus, the data suggest that at-home treatment in select

TABLE 5 Comparison of Current Study With Trials of DVT Treatment in an Outpatient Setting

	Present Study	Chong et al. 2005 ¹⁷	Ramacciotti et al. 2004 ¹⁸	Levine et al. 1996 ¹⁴
No. of patients	52	Enoxaparin 150 vs. UFH 148 (n = 298)	Enoxaparin 104 vs. UFH 97 (n = 201)	Enoxaparin 247 vs. UFH 253 (n = 500)
Treatment	Once-daily enoxaparin 1.5 mg/kg	Once-daily enoxaparin 1.5 mg/kg vs. UFH	Once-daily enoxaparin 1.5 mg/kg vs. UFH	Twice-daily enoxaparin 1 mg/kg vs. UFH
Study design	Prospective, open label, without a control group (1 center)	Randomized parallel-group, open-label (18 centers)	Randomized, controlled, open-label (13 centers)	Randomized open-label (14 centers)
Follow-up (days)	90	180	90-180	90
Incidence of major bleeding	1.9%	0%*	1.9% enoxaparin (n = 2), UFH (n = 3)	2.0% enoxaparin (n = 5), UFH (n = 3)
Overall incidence of DVT enoxaparin vs. UFH	0%	3.66%* enoxaparin 1.6% (n = 2), UFH 5.4% (n = 8)	3.48% enoxaparin 1% (n = 1), UFH 6% (n = 6)	6% enoxaparin 5.3% (n = 13), UFH 6.7% (n = 17)
Incidence of hospital readmission	1.9%	N/A	N/A	N/A

* 150 enoxaparin patients were evaluated for bleeding as a result of follow-up phone calls to patients; however, only 125 patients were evaluable for recurrent DVT because 20 had no efficacy assessment at 24 weeks, 6 received treatment for fewer than 5 days, and 3 did not satisfy entry criteria. The combined end point of DVT+PE was 2.7% for enoxaparin versus 8.8% for UFH ($P=0.026\%$).

DVT=deep vein thrombosis; PE=pulmonary embolism; N/A=not available; UFH=unfractionated heparin.

patients is a cost-effective alternative to hospitalization. This is supported by a previous study in which outpatient treatment with LMWH reduced the number of hospital days by 40% (7.2 vs. 12.1 days for UFH) and total treatment costs by 64% compared with UFH.⁹ Compared with UFH, LMWH treatment has been shown to produce cost savings when as few as 8% of patients with DVT were treated as outpatients.¹⁰ Moreover, studies comparing outpatient and inpatient treatment with LMWHs have shown that outpatient treatment can result in cost savings of up to 82%.^{11,19} Lee et al. reported in 1996 that the outpatient treatment of DVT with LMWH reduced the mean patient treatment cost from $\$3,266$ to $\$584$, a cost that included medications,

laboratory analyses, and home visits or hospital days as appropriate.¹¹ Tillman et al. found that an outpatient program carried out in a health maintenance organization, enrolling 391 patients treated with initial enoxaparin and warfarin to 90 days, realized total cost savings of \$1,108,587 over the 2-year evaluation period.²⁰

For patients with acute DVT, the American College of Chest Physicians (ACCP) recommends initial treatment with SC LMWH once or twice daily over UFH, as an outpatient if possible, or as an inpatient if necessary.²¹ Yet, despite the accumulating evidence for the safety and cost-effectiveness of at-home treatment with LMWHs, there appears to be some reluctance among physicians to use such therapy. More than 80% of patients with DVT have been shown to be eligible for outpatient treatment,^{22,23} yet one recent study reported that only 20% of the patients diagnosed with DVT received treatment with LMWH in an outpatient setting.²⁴ This may reflect physician concerns over the patient's ability to learn a new therapy (for self-administration) or the perceived lack of direct supervision by health care professionals. It may also reflect a view that findings from clinical trials, conducted under controlled conditions with multiple inclusion/exclusion criteria, are not necessarily applicable to the real-world patient population found in clinical practice.²⁵ Thus real-world studies, such as the one presented here, can provide important insights into the potential benefits of once-daily at-home treatment with LMWH for eligible patients.

Physician acceptance of at-home treatment appeared to improve during the course of this pilot study. Physicians began to contact the investigator to enroll patients and, in some cases, sent patients to the emergency room for consideration for home care as a substitute for hospital admission. This has particular significance given that DVT has traditionally been perceived by physicians as a serious condition requiring hospitalization. Furthermore, in the early stages of this pilot study, the daily patient assessments by the home-care nurse helped convince the physicians of the safety of home treatment, such that toward the end of patient enrollment, physicians were suggesting that patients be taught to self-inject enoxaparin to avoid the need for nursing visits. This could be explored further in future studies. While the home-care nurse confirmed compliance with the medications, it may be beneficial to study daily compliance in patients trained to self-inject enoxaparin.

Limitations

Foremost among the limitations of this study is the lack of a UFH comparison arm with patients matched for disease severity. This limits clinical interpretation of our data and more robust cost-savings analysis. Second, the relatively small sample size and exclusion of high-risk patients limit the generalization of these results to all patients with DVT. Third, assessment of DVT recurrence was based on patient self-assessment and was not subject to objective screening. Fourth, the questionnaire used in

this study was intended as an indicator of patient satisfaction and did not provide a validated quality-of-life assessment or quantitative measure of patient satisfaction. Further studies examining the service/humanistic outcomes of care for DVT would be of value in supporting once-daily home management of DVT.

Conclusion

Initial once-daily enoxaparin administered in the home with concurrent warfarin appears to provide efficacious and safe care in eligible patients with acute DVT. Home treatment with enoxaparin offers the opportunity to reduce the cost of treating DVT, without compromising clinical outcomes, and may be associated with patient satisfaction with care. This was a pilot study, and the favorable clinical and service/humanistic outcomes observed should be assessed with more quantitative measures by other researchers.

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