Deep Venous Thrombosis

Outpatient Management of Acute Deep Venous Thrombosis

Case Study and Commentary, Victor F. Tapson, MD

INSTRUCTIONS

The following article, “Outpatient Management of Acute Deep Venous Thrombosis,” is a continuing medical education (CME) article. To earn credit, read the article and complete the CME evaluation form on page 71.

OBJECTIVES

After participating in the CME activity, primary care physicians should be able to:
1. Discuss the efficacy and safety of low-molecular-weight heparin (LMWH) and unfractionated heparin for treatment of deep venous thrombosis (DVT)
2. Evaluate the benefits of outpatient versus inpatient therapy
3. Describe components of an outpatient treatment program for DVT
4. Discuss economic aspects of treatment with LMWH

Venous thromboembolism (VTE) represents a spectrum of disease that includes deep venous thrombosis (DVT) and pulmonary embolism (PE). Both DVT and PE are frequently clinically unsuspected, leading to significant diagnostic and therapeutic delays and accounting for substantial morbidity and mortality. An estimated 600,000 cases of VTE occur annually; however, more than half of these are never diagnosed [1].

Although many patients who die from acute PE have coexisting terminal illnesses, this disease entity is responsible for the deaths of approximately 50,000 to 100,000 patients with an otherwise good prognosis, and many of these deaths would appear to be preventable [2,3]. It is crucial that clinicians know the risk factors for and recognize the symptoms of DVT and/or PE so that appropriate diagnostic testing and therapy can proceed as quickly as possible, as anticoagulation has been shown to reduce mortality in this disease. When DVT or PE are diagnosed or strongly suspected, parenteral anticoagulation should promptly be instituted unless contraindications exist. Confirmatory diagnostic testing should be undertaken if anticoagulation is to be continued. Standard unfractionated heparin (UFH) and low-molecular-weight heparin (LMWH) exert a prompt antithrombotic effect preventing thrombus growth, allowing the fibrinolytic system to act unopposed and more readily reduce the size of the thromboembolic burden [4].

Until recent years, patients with acute DVT were most commonly treated as inpatients with a bolus of UFH followed immediately by a continuous intravenous infusion of heparin. More recently, stable patients presenting with DVT with or without PE at many institutions are evaluated in the clinic or emergency department (ED) and, if they meet specific criteria, discharged and treated entirely in the outpatient arena. One institution’s approach to outpatient DVT treatment is described in the primer that begins on page 64.

CASE STUDY

Initial Presentation

A 66-year-old man with chronic obstructive pulmonary disease (COPD) presents to the ED for evaluation of pain and swelling in the left calf.

History

Five days ago, the patient developed an acute COPD flare with increased cough, sputum production, wheezing, and dyspnea. He was started on antibiotics and a steroid taper and sent home. He was much less mobile than at baseline, walking only from bed to bathroom and back for the next 3 days. On the fourth day, he noted the onset of pain and swelling in the left calf, which has increased over the past 24 hours.

Physical Examination

The patient is alert, oriented, and comfortable-appearing at rest. Heart rate is 88 bpm, respiratory rate is 18 breaths/min, and blood pressure is 140/78 mm Hg. The patient is afebrile. Lung examination reveals diffusely decreased breath sounds and a few rhonchi at both bases. Heart sounds are distant, as is consistent with COPD. Examination of the extremities reveals a tender, swollen left calf. Results from a complete blood count, chemistry panel, and coagulation studies are normal.

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Diagnosis
A compression ultrasound reveals DVT in the popliteal vein extending into the superficial femoral vein.

- What therapies are available for treatment of DVT?

Unfractionated Heparin
As mentioned, traditionally DVT is treated with UFH administered by continuous intravenous infusion. A secure continuous intravenous line is necessary for optimal delivery of UFH in the treatment setting and this may require replacement once or more during the 5- to 7-day course of UFH. The activated partial thromboplastin time (aPTT) must be aggressively followed at 6-hour intervals until it is consistently in the therapeutic range of 1.5 to 2.0 times control values [4]. This range corresponds to a heparin level of 0.2 to 0.4 U/mL as measured by protamine sulfate titration. In general, heparin should be administered as an intravenous bolus of 5000 U followed by a maintenance dose of at least 30,000 to 40,000 U per 24 hours by continuous infusion [5]. The lower dose is administered if the patient is considered at high risk for bleeding. This aggressive approach decreases the risk of subtherapeutic anticoagulation and therefore of VTE recurrences, and although supratherapeutic levels are sometimes achieved initially, bleeding complications do not appear to be increased [6]. More recent data continues to support the principle that if UFH is to be used, it should be used aggressively. An alternative regimen consisting of a bolus of 80 U/kg followed by 18 U/kg/hr has been recommended [7]. Further adjusting of the heparin dose should also be weight-based. This weight-adjusted approach is recommended in recent guidelines from the American College of Chest Physicians (ACCP) Consensus Conference on Antithrombotic Therapy [8].

Low-Molecular-Weight Heparins
With the advent of LMWH preparations, treatment of acute DVT has been dramatically altered. While traditionally DVT is treated with UFH administered by continuous intravenous infusion, LMWH preparations allow for subcutaneous administration once or twice daily depending on the drug and the specific indication. The bioavailability of LMWH ensures a predictable dose response and eliminates the need for monitoring in most patients. (In patients with significant obesity, renal insufficiency, or weight less than 40 kg, monitoring is recommended via measurement of anti-factor Xa levels.) Additional advantages of using LMWH for the treatment of DVT are listed in Table 1.

Trials Comparing LMWH with UFH
A number of clinical trials have compared LMWH preparations with UFH in patients with VTE [9–11]. In 1996, the results of 2 large (Canadian and European) trials were reported in the same issue of the New England Journal of Medicine [9,10]; the studies showed that out-of-hospital administration of LMWH to eligible patients with DVT was as effective and safe as UFH. In both studies, the 2 study groups did not demonstrate any statistically significant differences in clinical endpoints such as recurrent thromboembolic disease, major bleeding, or death. A number of other outpatient studies followed these 2 pivotal trials. Four meta-analyses examined the use of LMWH compared with unfractionated heparin for the initial treatment of acute proximal DVT [12–15]. While there was overlap with regard to the studies included in these analyses, they helped to confirm the efficacy and safety of LMWH for the treatment of established DVT. The most recent of these meta-analyses suggested a reduced total mortality in patients treated with LMWH, but the precise reason for this is not clear. [12].

Available Agents
There are 2 LMWH preparations approved by the U.S. Food and Drug Administration (FDA) for use in patients presenting with DVT with or without acute PE. Enoxaparin is approved for both inpatient and outpatient use at a dose of 1 mg/kg subcutaneously every 12 hours or at 1.5 mg/kg once daily for inpatient use. The latter regimens were studied in a large randomized controlled trial of inpatients in which both doses proved as effective and safe as unfractionated heparin [16]. The second preparation, tinzaparin, is administered as 175 U once daily, with the FDA approval being based on clinical trials involving inpatients. Neither enoxaparin nor tinzaparin is approved for use in patients presenting with acute PE, although tinzaparin has proven effective in a large, randomized European trial of patients

Table 1. Advantages of Low-Molecular-Weight Heparin Over Standard Unfractionated Heparin

<table>
<thead>
<tr>
<th>Advantage</th>
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<tr>
<td>Superior bioavailability</td>
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<tr>
<td>Superior or equivalent safety and efficacy</td>
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<tr>
<td>Subcutaneous once- or twice-daily dosing</td>
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<tr>
<td>No laboratory monitoring*</td>
</tr>
<tr>
<td>Less phlebotomy (no monitoring/no intravenous line)</td>
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<td>Less thrombocytopenia</td>
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<tr>
<td>Earlier/facilitated ambulation</td>
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<td>Ease of outpatient therapy</td>
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<tr>
<td>Based on above, time saved for nursing staff</td>
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<td>Based on above, increased patient satisfaction</td>
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*For treatment of established deep venous thrombosis ± pulmonary embolism, monitoring of anti-Xa levels should be considered in massively obese patients, patients weighing less than 40 kg, and patients with renal insufficiency.
with PE [17]. It would appear logical that since DVT and PE represent 2 manifestations of the same disease, LMWH would be as effective for acute PE as standard UFH. Steps outlining the use of LMWH as outpatient therapy for acute DVT derived from the Sixth ACCP Antithrombotic Therapy Consensus Statement are listed in Table 2 [8].

Currently, both subcutaneous LMWH and UFH by continuous intravenous infusion are utilized for the treatment of inpatients with established VTE. The advantages to using LMWH for acute DVT in the outpatient setting also apply when using it in the inpatient setting. Advantages, however, to using intravenous UFH over LMWH for treatment of acute DVT include UFH’s short half-life (allowing necessary surgical procedures to be performed after only about 4 to 5 hours following infusion discontinuation) and lower cost, although data is accumulating indicating that even in the inpatient setting, overall cost may be lower with LMWH (see cost-effectiveness discussion below).

- **Is this patient a candidate for outpatient treatment?**

It is important to carefully evaluate each patient with DVT prior to discharging on outpatient therapy. Patients should be stable, compliant, and have no signs of symptomatic PE. (Although outpatient therapy of symptomatic, stable PE patients with LMWH has been evaluated, it is not commonly practiced in the United States.)

In addition to PE, there are several other risk factors that deem a patient not well-suited to outpatient care. For example, patients with very extensive, symptomatic proximal DVT or with unstable comorbid illness should be considered for inpatient therapy. The Lovelace Health Systems outpatient DVT treatment protocol described in the primer identifies a set of exclusionary criteria; these are listed in the Table on page 66. If teaching cannot be completed within a reasonable period of time in the emergency department, if clinical stability cannot be assured, or if another reason for admission is evident, the patient can be admitted for a 24- to 48-hour hospital stay and then discharged to complete therapy in the outpatient setting.

**Initiation of Therapy**

There is no history of bleeding disorders, recent surgery, or other contraindications to anticoagulation. The patient’s laboratory tests are normal. His acute obstructive lung disease flare has improved significantly and does not constitute a reason for admission. No invasive procedures are anticipated; in the setting of treatment of acute DVT, this would have favored the use of UFH. Based on evaluation by the ED physician and the nurse responsible for patient education, the patient is judged to be a good outpatient candidate. It is therefore elected to treat the patient on an outpatient basis.

The patient is instructed on subcutaneous injection, begun on LMWH, and discharged to home. The patient is instructed to return to the anticoagulation clinic or ED for immediate evaluation if increased pain or swelling of the leg develops or any bleeding occurs. Oral warfarin is started the following day. The patient lives 15 miles from the hospital. He returns to the anticoagulation clinic for protime/international normalized ratio (PT/INR) testing 2 days later.

- **What is follow-up care for patients receiving outpatient DVT therapy?**

Documented proximal DVT or PE should be treated for at least 3 months. Longer treatment is appropriate when significant risk factors persist or when patients have idiopathic DVT. Both short- and long-term anticoagulation guidelines are outlined in the ACCP consensus conference on antithrombotic therapy [8].

If pain and swelling are significant, minimizing ambulation may be appropriate. However, based on clinical trial data, bed rest in patients being treated for acute DVT probably does not reduce the incidence of acute PE [18].

- **How cost-effective is treatment of DVT with LMWH?**

Treatment of DVT with LMWH is more cost-effective than treatment with UFH. O’Brien and colleagues [19] performed
an economic analysis of the Levine et al outpatient DVT study [9] and determined that the cost of outpatient therapy compared with inpatient therapy with standard heparin was approximately $3000 less per patient (P < 0.001). Eliminating the need for hospitalization substantially reduces the cost of care. Overall cost in patients treated with LMWH in the inpatient setting also has proven lower than with intravenous UFH in several clinical trials. In a meta-analysis, Rodger and colleagues [20] compared the cost of inpatient UFH, inpatient LMWH, inpatients treated with UFH who were eligible for outpatient therapy, and outpatients treated with LMWH. While outpatients treated with LMWH incurred the lowest cost, it was determined that the cost of treating inpatients with LMWH was less than that for inpatients treated with UFH, although the latter difference was not significant. Gould et al [21] similarly determined that the cost of inpatient treatment of DVT was not statistically different in patients receiving UFH compared with LMWH. Finally, a retrospective analysis of the Merli study [16] of inpatient LMWH versus standard heparin also revealed similar costs among the 3 groups of patients (intravenous UFH and subcutaneous enoxaparin either once or twice daily) [22]. The additional cost of enoxaparin was offset by a lower hospital readmission rate and shorter readmission length of stay.

**Treatment Course**

On day 5 of LMWH therapy, the INR returns therapeutic (> 2.0) for a second consecutive day, and the therapy is discontinued. Warfarin is continued for 6 months with periodic INR checks. The patient experiences no complications.

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**References**

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EVALUATION FORM: Outpatient Management of Acute Deep Venous Thrombosis

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Part 1. Please respond to each statement.

I was provided with new information pertinent to my practice
I reaffirmed a specific skill or knowledge.
This article will help with clinical decision making.
Relevant clinical outcomes are addressed.
The case is communicated in a manner that kept my interest.
The case presentation is realistic and effective.
I could easily interpret the tables and figures.
My attitude about this topic changed in some way.

Additional comments:

Part 2. Please complete the following sentence.

As a result of reading this case study, I . . .

see no need to change my practice.
will seek more information before modifying my practice.
intend to change the following aspect(s) of my practice: (Briefly describe)


Signature: ______________________ Date: ______________________

Part 4. Identifying information: Please PRINT legibly or type the following:

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_____________________________ Social Security number: ____________________

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