Expanding Eligibility for Outpatient Treatment of Deep Venous Thrombosis and Pulmonary Embolism With Low-Molecular-Weight Heparin

A Comparison of Patient Self-Injection With Homecare Injection

Philip S. Wells, MD, FRCPC; Michael J. Kovacs, MD, FRCPC; Janis Bormanis, MD, FRCPC; Melissa A. Forgie, MD, FRCPC; Donna Goudie, RN; Bev Morrow, RN; Judy Kovacs, RN

Background: The outpatient treatment of patients with deep vein thrombosis and pulmonary embolism using low-molecular-weight heparin has the potential to reduce health care costs, but it is unclear if patients with deep vein thrombosis and pulmonary embolism can be treated as outpatients. In the published studies, more than 50% of patients were excluded from outpatient treatment for reasons such as comorbid conditions, short life expectancy, concomitant pulmonary embolism, and previous deep vein thrombosis, and many patients were not treated entirely at home. We sought to determine if expanding patient eligibility for the outpatient treatment of deep vein thrombosis and pulmonary embolism affects the safety and effectiveness of the treatment, and to determine if patient self-injection compared with injections administered by a homecare nurse affects these outcomes.

Patients and Methods: We treated as outpatients all patients with deep vein thrombosis and pulmonary embolism, except for those with massive pulmonary embolism, high risk for major bleeding or an active bleed, phlegmasia, and patients hospitalized for reasons that prevented discharge. We compared 2 models of outpatient care to determine feasibility, safety, and efficacy. Both models involved nurse managers who provided daily patient contact and ongoing treatment; however, in one model the patients were taught to inject themselves and in the other model homecare nurses administered the injections. We expanded the population of patients eligible for outpatient treatment by including many patients not treated at home in previous studies. Most patients in our study were treated with dalteparin sodium, 200 U/kg every 24 hours, for a minimum of 5 days. Therapy with warfarin sodium was started on the day of diagnosis or the following day. Patients were followed up for 3 months to determine rates of recurrent venous thromboembolism, bleeding, and death.

Deep Vein Thrombosis has a lifetime incidence of 2% to 5%, and 15,000 to 20,000 Canadians develop this illness each year.1 Deep vein thrombosis can result in considerable morbidity and, especially if untreated, mortality due to pulmonary embolism.2 The treatment for these disorders has required hospital admission for the administration of intravenous unfractionated heparin, but 2 recent studies demonstrate that outpatient treatment is safe and effective in selected patients.3,4 In these studies, low-molecular-weight heparin was administered subcutaneously. However, the results of these studies cannot necessarily be translated into practice because

Results: In this study, 194 (83%) of 233 consecutive patients were deemed eligible and treated as outpatients. Of the 39 patients who did not receive home therapy, 20 had concomitant medical problems responsible for their admission or were already inpatients, 6 had massive pulmonary embolism, 6 refused to pay for the dalteparin therapy, 4 had active bleeding, and 3 had phlegmasia cerulea dolens, which required treatment with intravenous narcotics for pain control. More than 184 (95%) of the 194 patients were treated entirely at home. There was no significant difference (P > .99) in the rate of recurrent venous thromboembolic events between the patients who were injected by homecare nurses (3/95 [3.2%]) and those who injected themselves (4/99 [4.0%]). Combining the 2 models, the overall recurrent event rate was 3.6% (95% confidence interval, 1.3%-7.4%). Similarly, there were no significant differences in rates of major hemorrhage (2/95 vs 2/99; P > .99), minor hemorrhage (8/95 vs 2/99; P = .06), and death (6/95 vs 8/99; P = .63). The overall rate of major hemorrhage was 2.0% (95% confidence interval, 0.6%-5.2%).

Conclusions: We demonstrate that more than 80% of patients at our tertiary care hospital could be treated at home using 1 of the 2 models of care we describe. Our results demonstrate that patients can safely and effectively perform home self-injection under the supervision of a hospital-based nurse. Injections at home by a homecare nurse are similarly effective. Our overall rates of recurrent venous thromboembolism, bleeding, and death are at least as favorable as those previously reported despite using 1 dose per day of dalteparin for most patients.

Arch Intern Med. 1998;158:1809-1812
PATIENTS AND METHODS

PATIENTS

All patients who presented to 2 university-based hospitals in Ontario (the Ottawa Civic Hospital, Ottawa, and the London Health Sciences Center, London) between February 1996 and November 1996 with objectively diagnosed (via ultrasonography or venography) deep vein thrombosis were considered eligible for outpatient treatment, and in the latter half of the study, patients with pulmonary embolism were also deemed eligible. We excluded patients with the following characteristics: (1) illness unrelated to venous thromboembolism for which the patient would require hospitalization for more than 48 hours; (2) active bleeding; (3) inpatient status without discharge in the next 48 hours; (4) pulmonary embolism if accompanied by hemodynamic instability or pain requiring intravenous narcotics or necessitating oxygen therapy to maintain oxygen saturation greater than 90%; (5) deep vein thrombosis if accompanied by pain requiring intravenous narcotics; (6) age younger than 18 years; or (7) the likelihood of poor compliance. The study protocol was approved by our institutional review boards and consent was obtained from all patients.

TREATMENT PROGRAM

All patients were treated with 100 U/kg of subcutaneous dalteparin sodium (Fragmin, Pharmacia-Upjohn, Mississauga, Ontario) twice daily, or 200 U/kg of dalteparin sodium once daily. After the first 38 patients, the twice-daily dose of dalteparin was replaced with a once-daily dose to simplify the treatment program. The first dose was given as soon as deep vein thrombosis or pulmonary embolism was diagnosed. Dalteparin was administered for a minimum of 5 days and not discontinued until the patient’s international normalized ratio was greater than 2.0 or 1.9 for at least 2 consecutive days. If patients still had considerable pain on day 3, therapy could be prolonged. Treatment with warfarin was started within 24 hours of the first dose of dalteparin (usually the same day), with the dose adjusted by the physician. In both centers, a nurse who had knowledge of venous thromboembolic disease coordinated patient care for the first 5 days. The nurse educated the patient (and the care provider when applicable) in a specialized hospital education unit with individualized teaching sessions, and explained patient and family responsibilities for assessment and self-monitoring at home. At the end of the session, the patients were given a written educational package (available on request) summarizing the teaching session and serving as a reference for family members. All patients were given an emergency number to call 24 hours a day if problems with bleeding or suspected recurrent thromboembolism arose. In the unlikely event that patients were unable to reach physicians, we advised them in their written package to report to the emergency department or to call an ambulance immediately. The nurse arranged with the patients to have their blood taken starting on day 2 or 3 to determine their international normalized ratios. Daily telephone contact was maintained by the nurse to assess the patient’s progress, communicate the dosage of warfarin ordered by the physician, and determine any adverse effects or symptoms. If the nurse determined that the patient had problems and deemed (either independently or after consultation with the physician) that the physician should assess the patient, then the patient came to the ambulatory thromboembolism unit for assessment or, if the patient was not ambulatory, an ambulance was arranged for a hospital visit. The frequency of such visits was recorded. The patients had access to the nurse or physician during the 3-month follow-up period and were instructed to report any signs or symptoms of recurrent deep vein thrombosis or pulmonary embolism and bleeding. All patients were to return 3 months after the initiation of therapy for a progress report and a repeat ultrasonographic examination.

The care between the 2 centers differed in that at one center (Ottawa Civic Hospital) the nurse taught the preparation and process of subcutaneous dalteparin injections. In this center, an attempt was made in all cases to have the patient or caregiver administer the injections. In addition, the nurse supervised all patient care as the primary contact person for the 3-month follow-up period. In the other center, the nurse or physician arranged for a homecare professional to visit the patient daily and administer the injections of dalteparin. The Ottawa Civic Hospital will be referred to as the self-injection center and the London Health Sciences Center will be referred to as the homecare injection center.

ANALYSIS

Recurrent deep vein thrombosis, pulmonary embolism, and bleeding events were compared between the 2 centers using the Fisher exact test (2-tailed). Death rates were compared using an uncorrected $\chi^2$ test. In addition, we determined the combined overall rates of outcome events and their 95% confidence intervals (CIs) according to the binomial distribution. All patient complaints that could have been due to bleeding, deep vein thrombosis, or pulmonary embolism were investigated with objective tests as elaborated below. We assessed bleeding by measuring hemoglobin levels, with further investigations dependent on the suspected cause of the bleeding. Bleeding was classified according to previously published criteria. The assessment of recurrent events was standardized. Venous ultrasonographic imaging or venography was mandatory in cases of suspected deep vein thrombosis, and confirmatory venography was required if the results of the ultrasound were equivocal. In patients with suspected pulmonary embolism, a ventilation-perfusion lung scan was initially performed. If results from the scan were normal, pulmonary embolism was ruled out, and if they were high, the probability of pulmonary embolism was confirmed. In all other cases, further diagnostic testing was required, including venous ultrasonographic imaging followed by venography or angiography if findings from the ultrasound were normal. Most patients with deep vein thrombosis were excluded in one study, and outpatient treatment was provided to less than half the patients randomized to receive therapy at home in the other. Furthermore, the patients were cared for in a highly supervised research setting. Care to patients who have not been recruited and monitored within the rigorous structure of a research setting has not been assessed.
Table 1. Baseline Characteristics of Patients Enrolled in Outpatient Treatment

<table>
<thead>
<tr>
<th>Event</th>
<th>Homecare</th>
<th>Self-Injection</th>
<th>Overall</th>
</tr>
</thead>
<tbody>
<tr>
<td>Proximal DVT</td>
<td>21</td>
<td>23</td>
<td>44 (23)</td>
</tr>
<tr>
<td>Pulmonary embolism</td>
<td>14</td>
<td>15</td>
<td>29 (15)</td>
</tr>
<tr>
<td>Arm DVT</td>
<td>2</td>
<td>4</td>
<td>6</td>
</tr>
<tr>
<td>Idiopathic</td>
<td>28</td>
<td>32</td>
<td>60 (31)</td>
</tr>
<tr>
<td>Cancer</td>
<td>32</td>
<td>29</td>
<td>61 (31)</td>
</tr>
<tr>
<td>Previous DVT</td>
<td>14</td>
<td>15</td>
<td>29 (15)</td>
</tr>
<tr>
<td>DVT due to risk factors</td>
<td>21</td>
<td>23</td>
<td>44 (23)</td>
</tr>
</tbody>
</table>

*All data are presented as No. (percentage) of patients unless otherwise noted. DVT indicates deep vein thrombosis; NA, not applicable.

Table 2. Recurrent Venous Thromboembolism, Bleeding, and Deaths in Patients Enrolled in Outpatient Treatment

| Event                        | Homecare | Self-Injection | P Value | Overall |
|------------------------------|----------|----------------|---------|
| Bleeding                     | 34       | 4              | .03     | 7 (3.6) |
| Minor                        | 8        | 2              | .06     | 16 (5)  |
| Major                        | 2        | 2              | .64     | 4 (2)   |
| Death                        | 6        | 8              | .63     | 14 (7)  |
| Metastatic cancer            | 4        | 7              | .06     | 11 (5)  |
| Sepsis                       | 0        | 1              | .06     | 1 (0.5) |
| Myocardial infarction        | 1        | 0              | .06     | 1 (0.5) |
| Sudden                       | 1        | 0              | .06     | 1 (0.5) |

*All data are presented as number (percentage) of patients. Ellipses indicate not calculated.

To determine the necessity of evaluating patient care outside of a research setting before it could be widely implemented, we first conducted a survey of hematologists and internists in Canada. It has already been demonstrated that effective continuity of care on an outpatient basis requires inclusion of the patient and family in the planning process, the designation of a specific professional to coordinate services, and the maintenance of patient contact beyond the period of acute illness. This information and our survey results led us to evaluate outpatient therapy in 2 tertiary care centers using 2 nurse-based models. In one center, community homecare nurses gave the patients injections. In the other center, patients were taught to inject themselves, while nurses supervised the entire 3 months of patient care and served as the primary contact person. The goals of our study were to expand the eligibility for outpatient care to include patients excluded in previous studies, to enroll patients with pulmonary embolism in outpatient care, and to determine if safety and efficacy differed between the 2 models of treatment.

RESULTS

In the 10-month study period, 194 (83%) of the 233 consecutive eligible outpatients were treated at home. Of the 39 patients who did not receive home therapy, 20 had concomitant medical problems responsible for their admission or were already inpatients, 6 had massive pulmonary embolism, 6 refused to pay for the dalteparin therapy, 4 had active bleeding, and 3 had phlegmasia cerulea dolens, which necessitated the administration of intravenous narcotics for pain control. Of the 194 patients treated at home, 48% were men and 52% were women. One hundred sixty-six patients received 1 dose of dalteparin per day, and more than 184 (95%) of the outpatients received their treatment entirely at home. Only 14 patients received prolonged therapy with dalteparin. In the 2 centers combined, 49% of patients injected themselves (20% of these individuals were injected by a caregiver), and a homecare registered nurse injected 51%. The mean age of the patients was 63.5 years (range, 19-92 years) in the homecare injection center and 63.1 years (range, 18-85 years) in the self-injection center. In the 2 centers combined, 154 patients had proximal deep vein thrombosis, 34 had pulmonary embolism, and 6 had axillary/subclavian vein thrombosis. Of these thromboembolic events, 60 were idiopathic, 61 were secondary to cancer, and 44 were secondary to other risk factors. In addition, 29 patients had a history of previous deep vein thrombosis. There were no significant differences in these characteristics between the 2 centers (Table 1). More than 184 (95%) of the 194 patients were treated entirely at home; the other patients were hospitalized for less than 72 hours (admitted because they presented on weekends when the study nurse was not available). There was no significant difference (P = .93) in the rate of recurrent venous thromboembolic events between patients at the homecare injection center (4/95 [4.0%]) and patients at the self-injection center (4/99 [4.0%]). The overall recurrent event rate was 3.6% (95% CI, 1.5%-7.4%). Similarly, there were no significant differences in rates of major hemorrhage (2/95 vs 2/99; P = .64), minor hemorrhage (8/95 vs 2/99; P = .06), and death (P = .63; 6/95 vs 8/99) between patients at the 2 centers. Eleven deaths were due to metastatic cancer, 1 each from sepsis and myocardial infarction, and 1 sudden death that was not believed to be due to pulmonary embolism (the cause of death could not be confirmed on autopsy) (Table 2). Only 1 patient had to stop treatment because of major hemorrhage. We were unable to determine any differences in reporting between the 2 centers that might have accounted for differences in the incidence of minor hemorrhage. There were 34 unscheduled follow-up visits at the homecare injection center and 29 at the self-injection center during the 3 months of follow-up (P = .60). Visits were for suspected recurrence in 82.4% (28/34) and 75.9% (22/29) of cases, respectively. Thirty percent of these visits were in the first 2 weeks of care. Ten percent of patients at the self-injection center refused or could not be taught self-injection.

COMMENT

Our study has shown the feasibility of providing outpatient care to most patients presenting to tertiary care hospitals with acute venous thromboembolic disorders.
We enrolled most patients with venous thromboembolism in our centers, expanding the indication for home therapy to a group of patients with more serious conditions than those previously described. We demonstrated that more than 80% of patients at our tertiary care hospital could be treated at home using 1 of the 2 models of care we describe herein. In the previous 2 outpatient studies, 30% to 75% of patients with venous thromboembolism were excluded from home therapy. In our study, there were no significant differences between the 2 centers for recurrent venous thromboembolism, bleeding, or death. Despite expanding the indication for therapy and enrolling patients with more critical conditions than those previously studied, we combined the results in our 2 patient groups to illustrate that the overall rates of recurrence (3.6%), major bleeding (2%), and death (7%) are similar to those previously reported; in the 2 studies described above, the pooled rates were 6.0%, 1.3%, and 5.6%, respectively. In these same studies, the pooled death rates in the patient population treated in hospital was 7.4%, which is similar to the incidence reported in our study. None of the deaths in our study occurred during the first 2 weeks of therapy. Without autopsies, it is impossible to be certain that none of the deaths were due to pulmonary embolism, but it only seemed possible in 1 case. In the study by Koopman et al, 1% of patients died of pulmonary embolism during the 3-month treatment period. It is inevitable that some patients will die during outpatient treatment, but it does not appear from the evidence at hand that this death rate is likely to exceed the death rate of inpatients treated for deep vein thrombosis and pulmonary embolism. Our results demonstrate that patients can safely and effectively perform home self-injection under the supervision of a hospital-based nurse. Injections at home by a homecare nurse are similarly effective. To date, there are no randomized studies comparing outpatient to in-hospital treatment in patients with pulmonary embolism. However, it is now widely accepted that pulmonary embolism and deep vein thrombosis are manifestations of the same disease, ie, many patients with pulmonary embolism have deep vein thrombosis and vice versa. In addition, we treated several patients with pulmonary embolism on an outpatient basis in a previous study. Therefore, we did not think it was inappropriate to enroll stable patients with pulmonary embolism in an outpatient treatment program. Given that these patients represent the minority of our patients, further studies may be indicated before this practice is widely implemented.

Our overall rates of recurrent venous thromboembolism, bleeding, and death are at least as favorable as those previously reported despite our use of 1 dose of dalteparin per day in most patients. Although other studies have used 1 dose of dalteparin per day, we enrolled a broader range of patients and provided outpatient care to most for the duration of therapy. Our study is the first to assess 2 different models of outpatient care. We have developed a program that can be adapted by a wide range of institutions. Although not formally assessed, the main barriers to implementing the program were the cost of dalteparin and the daily orders of warfarin. The former barrier can be addressed by the provision related to dalteparin on the Ontario Drug Benefit formulary or by homecare covering the cost. The latter barrier can be addressed by instructing patients to have their blood taken first thing in the morning (private laboratories will provide home visits for a small fee) and then to take warfarin with their evening meal. This allows the physician time to obtain the international normalized ratio result and contact the patient with dose changes.

Our study cannot determine the safety of outpatient care in smaller centers that treat fewer patients. However, our results suggest that adequate patient education, careful follow-up, and ready access to health care professionals are likely to result in program success. Patient self-injection is likely to be less costly to the health care system than using homecare nurses, but issues of patient anxiety and quality of life have not yet been addressed.

Accepted for publication September 30, 1997.

Dr Wells is the recipient of a Research Scholarship from the Heart and Stroke Foundation of Canada, Ottawa, Ontario.

Reprints: Philip S. Wells, MD, FRCPC, MSc, Suite 467, 737 Parkdale Ave, Ottawa, Ontario, Canada K1Y 1J8 (e-mail: pwells@civich.ottawa.on.ca).

REFERENCES