Length of Hospital Stay for Treatment of Deep Venous Thrombosis and the Incidence of Recurrent Thromboembolism

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Background: Current guidelines suggest that all patients with acute deep venous thrombosis should be treated with intravenous heparin for at least 5 days, overlapping with warfarin sodium for 4 to 5 days.

Methods: Using linked state of California hospital discharge records from 1991 to 1994 we identified patients with acute deep venous thrombosis without pulmonary embolism, and determined the 6-month cumulative incidence of rehospitalization for recurrent thromboembolism. Coding was validated by reviewing the charts of 218 patients matched with the statewide data from 4 local hospitals.

Results: A total of 36,924 linked records met study criteria. In the validation group, objectively confirmed thrombosis that was treated with intravenous heparin followed by warfarin was noted in 20%, 65%, 94%, and 95% of the patients who were hospitalized for 2 or fewer days or 3, 4, or 5 or more days, respectively. Statewide, among patients hospitalized for 3, 4, 5, and 6 days, the 6-month cumulative incidence of hospitalization for recurrent thromboembolism was 5.4%, 5.1%, 5.4%, and 6.0%, respectively. Multivariate modeling of patients hospitalized for 3 to 10 days revealed that recurrent thromboembolism was associated with the length of hospitalization (odds ratio [OR], 1.06 each additional day; 95% confidence interval [CI], 1.04-1.08), presence of malignancy (OR, 1.58; 95% CI, 1.46-1.68), age (OR, 0.85 each 10 years; 95% CI, 0.84-0.86), dementia (OR, 0.38; 95% CI, 0.26-0.49), hospitalization for multiple injuries within 3 months (OR, 0.46; 95% CI, 0.32-0.60), and surgery within 3 months (OR, 0.84; 95% CI, 0.78-0.90).

Conclusions: We found no evidence that a stay of 4 days for treatment of deep venous thrombosis was associated with a higher rate of recurrent thromboembolism compared with hospitalization for 5 or more days. Although the evidence was not as strong, the incidence of recurrent thromboembolism after a stay of 3 days appeared comparable with that after a stay of 5 days. These findings suggest that fewer than 5 days of intravenous heparin overlapping with warfarin may provide effective initial treatment for deep venous thrombosis among patients deemed ready for hospital discharge.

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SUBJECTS AND METHODS

DISCHARGE COHORT

This study was approved by the California Health and Welfare Agency Committee for the Protection of Human Subjects and the University of California, Davis, Human Subjects Committee in Sacramento. We used a linked hospital discharge data set compiled by the California Office of Statewide Planning and Development (OSHPD) to determine the incidence and date of recurrent thromboembolic events. All nonfederal licensed hospitals, both acute care and rehabilitation hospitals, are required by the state of California to submit information about each inpatient after hospital discharge that include the admission and discharge date, birth date, race, ZIP code of residence, Social Security number, and sex. In addition, OSHPD requires that hospitals report the principal diagnosis (reason prompting the admission) and up to 24 additional diagnoses, the principal procedure and up to 20 additional procedures, the date of each procedure, and the discharge disposition (eg, home or death). All diagnoses and procedures are coded using the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM). Since July 1, 1990, it has been possible to link serial hospital records for nearly all California residents using encrypted Social Security numbers, except for patients using out-of-state or federal hospitals.

The OSHPD defines the length of hospitalization as the difference between the admission date and the discharge date. Thus, 1 day of hospitalization means that the patient was discharged the day after admission, which represents, for example, a stay of 1 to 48 hours and 2 days means 25 to 72 hours. Because transfer to another hospital or health care facility would artificially shorten the length of stay at the first hospital, we defined length of hospitalization as the total number of days of contiguous inpatient care. Deaths were determined using the discharge disposition code and a linked death registry.

PATIENTS

We included in our cohort only patients admitted to the hospital for acute deep venous thrombosis who were not coded as having pulmonary embolism. We included only patients with a diagnosis related group of 128, 130, or 131 (consistent with a principal diagnosis of venous thrombosis without major surgery), and a principal diagnosis of venous thrombosis defined by ICD-9-CM codes 451.1x, 451.2, 451.81, 451.9, 453.1, 453.2, 453.8, 453.9, or 997.2 (postoperative complication, if accompanied by a secondary diagnosis of venous thrombosis). We excluded patients who had a secondary diagnosis of pulmonary embolism (ICD-9-CM code 413.1). The diagnosis related group requirement was designed to exclude patients who underwent major surgery during the index hospitalization, which might have prevented standard anticoagulation treatment. We analyzed the length of hospital stay for all patients hospitalized in 1991 through 1994, but restricted our outcome analysis to patients hospitalized between January 1, 1991, and June 30, 1994, allowing a minimum of 6 months’ follow-up. We analyzed only the first hospitalization for venous thrombosis in each linked record and, to minimize the likelihood that patients were being treated for venous thrombosis with warfarin at the cohort’s inception, we excluded patients diagnosed (principal or secondary) as having pulmonary embolism or venous thrombosis in the 6 months before the index hospitalization. Finally, we excluded patients treated during the index hospitalization with an inferior vena cava filter (ICD-9-CM code 38.7).

We defined several conditions associated with deep venous thrombosis, including cancer (ICD-9-CM codes 140 through 208, except code 173, nonsmall cell cancers); multiple trauma (2 ICD-9-CM codes between 800 and 959); lower extremity fracture (codes 820.x-828.0); fracture of records that met entry criteria. Clinical characteristics of the study cohort are shown in Table 1. The mean (± SD) length of hospitalization for deep venous thrombosis decreased progressively between 1991 and 1994, from 6.6 ± 2.5 days in 1991 to 5.7 ± 2.3 days in 1994 (P<.001). The percentage of patients hospitalized for 0 to 2 days was small, increasing from 4.2% in 1991 to 5.6% in 1994. Figure 1 shows the increases in the percentages of patients hospitalized for 3 or 4 days and 5 or 6 days during this period and the corresponding decreases in the percentages of patients hospitalized for 7 to 10 days and more than 11 days. Only 1.3% to 2.0% of all patients were transferred directly to another hospital or facility each year.

VALIDATION OF CODING AND LENGTH OF STAY

The charts of 218 patients who were matched with the OSHPD cohort and who were hospitalized at the University of California, Davis Medical Center (n = 76), the Kaiser Permanente Medical Center (n = 68), Sutter General Hospital (n = 35), or Sutter Memorial Hospital (n = 39), all located in Sacramento, were reviewed. Table 2 shows the percentage of patients with typical deep venous thrombosis in this cohort, stratified by length of hospitalization. Overall, of 218 patients, 191 (88%) had objectively defined deep venous thrombosis and 181 (83%) met criteria for typical venous thrombosis.

Outcomes were determined for the 32 059 patients hospitalized before June 30, 1994. Among the 30 560 patients hospitalized for 3 or more days, the cumulative incidence of rehospitalization for recurrent deep venous thrombosis or pulmonary embolism during the first 6 months of follow-up was 1800 (5.9%); 87% of the patients with recurrences had venous thrombosis and 13% had pulmonary embolism. Figure 2 shows the incidence of recurrent thromboembolism among patients hospitalized for 3 to 10 days. The 6-month incidence of recurrent thromboembolism was 110 (5.4%) of 2055 patients hospitalized for 3 days, 203 (5.1%) of 3993 patients hospitalized for 4 days, 283 (5.4%) of 5288 patients hospitalized for 5 days, and 335 (6.0%) of 5554 patients hospitalized for 6 days. Comparing hospital stays of 4 and 5 days, the difference
in the 6-month incidence of recurrent thromboembolism was 0.27% (95%, -0.64% to 1.18%); there was 80% power to detect a rate of recurrent thromboembolism as high as 6.5% in the 4-day group with \( \alpha = .05 \). In addition, the difference in the incidence of recurrent thromboembolism between patients hospitalized for 3 or 4 days (5.2%) and patients hospitalized for 5 or 6 days (5.7%) was not significant (difference = 0.53%; 95%, -0.18% to 1.23%).

In bivariate analyses, a higher incidence of recurrent thromboembolism was significantly associated with longer length of hospitalization and presence of malignancy, whereas age, dementia, hospitalization within 3 months for multiple injuries, trauma of the lower extremity within 3 months, and any surgery within the previous 3 months were associated with a lower incidence of recurrent thromboembolism. The following measures of comorbidity were not significantly associated with recurrent thromboembolism: renal disease, prior myocardial infarction, peripheral vascular disease, congestive heart failure, chronic obstructive pulmonary disease, diabetes, peptic ulcer disease, liver disease, rheumatic disease, paralysis, varicose veins, and a combined measure called the modified Charlson index. The results of stepwise multivariate logistic regression analysis among patients hospitalized for 3 to 10 days is shown in Table 3. With the exception of trauma of the lower extremity within 3 months, all the measures associated with recurrent thromboembolism in bivariate analyses entered the multivariate model, including longer length of hospitalization.

To explore the possibility that longer length of stay was serving as a proxy for illness severity, we performed logistic regression analysis using death within 6 months of initial hospitalization as the dependent variable, forcing the length of hospitalization in the model, and allowing all measures of comorbidity to enter in a stepwise fashion. In this model, length of stay was significantly associated with death within 6 months (odds ratio, 1.1 for each hospital day; 95% confidence interval, 1.09-1.13), together with 8 measures of comorbidity, such as presence of malignancy or liver disease. This finding suggests that in our analysis of recurrent thromboembolism, length of hospitalization may have served as a measure of comorbidity that we were unable to explain by ICD-9-CM codes.
COMMENT

Several important issues regarding the treatment of acute deep venous thrombosis remain poorly defined and therefore controversial. One such issue is the optimal duration of intravenous heparin therapy and the number of days that treatment with warfarin should overlap with heparin. There are a number of reasons why fewer than 5 days of heparin together with 4 to 5 days of warfarin might result in a higher incidence of recurrent thromboembolism in the first 6 months following discharge. First, although Hull and coworkers found no significant difference in the incidence of recurrent thromboembolism after 5 days of heparin therapy compared with 10 days, this small clinical trial of 200 patients had only 15% power to detect a 3% difference in the 6-month incidence of recurrent venous thromboembolism (eg, 7% vs 10%). Thus, a large trial might have shown that 5 days of heparin therapy is less effective compared with 10 days of heparin. Second, 2 studies have shown that the efficacy of warfarin depends on depletion of clotting factors X and II, both of which have long half-lives compared with factor VII, which is the principal factor that affects the INR. These findings provide the rationale for the recommendation that warfarin therapy be overlapped with heparin for at least 4 to 5 days, as well as the widely held view that an INR of 2.0 or higher during the first 2 or 3 days of warfarin therapy may not provide sufficient anticoagulation to prevent progression of thrombosis. Third, a clinical trial in the Netherlands found that oral anticoagulation therapy alone, without any heparin, was associated with a 3-fold higher 6-month incidence of recurrent venous thrombosis (20%) compared with combined therapy (7%).

There is some evidence suggesting that fewer than 5 days of heparin treatment may be as effective as treatment for longer periods, particularly if warfarin treatment is instituted early and an INR of 2.0 or higher is quickly achieved. In a study that detected microemboli flowing cephalad from acute deep venous thrombi, the emboli could not be detected after 72 hours of heparin therapy. Reduction in factor VII levels, as evidenced by an INR of 2.0 or higher, may be more important in inhibiting coagulation than a reduction in factor II or factor X levels. Studies have shown that the level of factor VII correlates with risk for ischemic heart disease, and factor VII activity correlates with activation of thrombosis, as measured using the activation product of prothrombin, F1+2.

In this study we used a large linked data set to determine the relationship between the duration of initial hospitalization for treatment of acute venous thrombosis and the incidence of rehospitalization for recurrent thromboembolism. Use of this linked data set allowed us to identify all subsequent hospitalizations within California, except when hospitalization occurred in a military or veterans hospital. Prior validation studies have shown high sensitivity and specificity for the coding of principal diagnoses. However, we were concerned about the accuracy of the coding for venous thrombosis among patients admitted for inexplicably short periods, particularly 0 to 3 days.

The concern that patients admitted for short periods would have atypical venous thrombosis proved to be warranted. In our validation study, only 5 of 20 patients hospitalized for 1 or 2 days had documented venous thrombosis that was treated with heparin and warfarin. Among 37 patients who were hospitalized for 3 days, 24 (65%) met our criteria for typical venous thrombosis. This

Table 1. Clinical Characteristics of the Study Cohort Stratified by Year

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<tbody>
<tr>
<td>Venous thrombosis cases, No.</td>
<td>9268</td>
<td>9184</td>
<td>9074</td>
<td>9298</td>
</tr>
<tr>
<td>Length of hospitalization, d</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>6.6 ± 2.5</td>
<td>6.3 ± 2.4</td>
<td>6.0 ± 2.4</td>
<td>5.7 ± 2.3</td>
</tr>
<tr>
<td>Median</td>
<td>6</td>
<td>6</td>
<td>6</td>
<td>5</td>
</tr>
<tr>
<td>Sex, No. (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>4265 (46)</td>
<td>4171 (46)</td>
<td>4181 (46)</td>
<td>4192 (46)</td>
</tr>
<tr>
<td>Female</td>
<td>5003 (54)</td>
<td>5013 (55)</td>
<td>4893 (54)</td>
<td>5106 (56)</td>
</tr>
<tr>
<td>Malignancy present, No. (%)</td>
<td>1261 (14)</td>
<td>1254 (14)</td>
<td>1362 (15)</td>
<td>1334 (15)</td>
</tr>
<tr>
<td>Recurrent thromboembolism within 6 mo, No. (%)</td>
<td>628 (6.8)</td>
<td>485 (5.3)</td>
<td>499 (5.5)</td>
<td>256 (5.5)*</td>
</tr>
<tr>
<td>Venous thrombosis</td>
<td>544 (87)</td>
<td>427 (88)</td>
<td>435 (87)</td>
<td>222 (87)*</td>
</tr>
<tr>
<td>Pulmonary embolism</td>
<td>84 (13)</td>
<td>58 (12)</td>
<td>64 (13)</td>
<td>34 (13)*</td>
</tr>
<tr>
<td>Dead within 6 mo, No. (%)</td>
<td>972 (10)</td>
<td>925 (10)</td>
<td>1065 (12)</td>
<td>533 (12)*</td>
</tr>
</tbody>
</table>

percentage was lower than that seen among patients hospitalized for 4 days (94%) or 5 or more days (95%). However, 29 (78%) of 37 of the validation patients hospitalized for 3 days were treated with warfarin and were presumably at risk for recurrent thromboembolism. The lower prevalence of typical venous thrombosis in patients hospitalized for 3 days could have biased the observed 6-month incidence of recurrent thromboembolism if atypical patients had a significantly lower risk of recurrent thromboembolism. The percentage of patients discharged with a therapeutic INR was similar among the patients with typical venous thrombosis who were treated for 3 or 4 days compared with 5 or more days, suggesting that physicians did not generally discharge patients early unless the INR was close to or higher than 2.0.

In our analysis of the state cohort we found that the incidence of rehospitalization for recurrent thromboembolism among patients hospitalized for 3 days (5.4%) or 4 days (5.1%) was approximately the same as the incidence among patients hospitalized for 5 days (5.4%). Because the patients in our validation cohort who were hospitalized for 4 days were similar to those who were hospitalized for 5 days (Table 2), our findings suggest that the 6-month incidence of recurrent thromboembolism is no higher for patients hospitalized for 4 days compared with hospitalization for 5 or more days. Assuming that one third of all patients statewide who were hospitalized for 3 days had atypical cases, and that none of these atypical cases developed recurrent thromboembolism, the true cumulative incidence among patients hospitalized for 3 days could have been as high as 8.3%. For the reasons cited above, the rate was likely to be much closer to the observed rate of 5.4%.

Overall, we found that there was a statistically significant, but probably clinically unimportant, increase in the 6-month incidence of rehospitalization for recurrent thromboembolism associated with longer duration of hospitalization. This paradoxical finding may be ex-
plained by the presence of confounding related to unmeasured illness severity or resistance to oral anticoagulation therapy. The significant association between length of stay and death within 6 months supports a relationship between length of hospitalization and greater comorbidity.

The 6-month incidence of recurrent thromboembolism that we observed, 5.9%, is consistent with the findings of other studies, which have reported 8.6%, 6.7%, and 5.1%, although the exact incidence depends on the prevalence of underlying risk factors for thrombosis as well as the adequacy of anticoagulant treatment. Our lower rate probably reflects some migration out of the state of California, loss of follow-up because of admission to a veterans or military hospital, and elimination of patients who underwent intervening surgery.

The predictors of recurrent thromboembolism that we noted in our multivariate model are similar to those found by Prandoni and coworkers, who followed up an inception cohort of 355 patients with venous thrombosis. This group noted that cancer, recent surgery, and recent trauma were associated with recurrent thromboembolism, with relative hazards of 1.72, 0.36, and 0.51, respectively. These values are similar to the odds ratios of 1.58, 0.84, and 0.46 that we noted for cancer, recent surgery, and recent trauma, respectively. It is not surprising that we found an odds ratio closer to 1.0 for recent surgery because we defined surgery based on diagnosis related group codes that included minor operations. Our finding that younger age was associated with greater odds of developing recurrent thrombosis has not been previously reported. This may reflect the higher rate of recurrent thromboembolism that has been noted among patients with idiopathic venous thrombosis, a condition seen more frequently in younger individuals. The close similarity between our findings and those of Prandoni et al indirectly supports the validity of our administrative data set.

In conclusion, using a large, linked administrative data set combined with a validation sample, we found that the percentage of patients with deep venous thrombosis who were hospitalized for fewer than 5 days increased significantly between 1991 and 1994. The 6-month cumulative incidence of rehospitalization for recurrent thromboembolism among patients hospitalized for 4 days to treat acute venous thrombosis was no higher than the rate noted among patients hospitalized for 5 days. Although the evidence was not as strong, it appeared that the incidence of recurrent thromboembolism among patients treated for 3 days was not substantially higher than that among patients treated for 5 days. These findings suggest that fewer than 5 days of intravenous heparin with overlapping warfarin therapy may provide effective initial treatment for patients with deep venous thrombosis who are judged to be ready for discharge from the hospital.

A randomized controlled trial would be necessary to provide a definitive answer to the question of whether fewer than 5 days of heparin therapy for treatment of acute deep venous thrombosis is safe and effective.

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REFERENCES