Challenges to the Effective Use of Unfractionated Heparin in the Hospitalized Management of Acute Thrombosis

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Background: Unfractionated heparin therapy is care intensive because of dose-response variability, and because of the necessity of constant intravenous infusion and frequent monitoring. We sought to assess the real-world course of transition from heparin to warfarin in hospitalized patients undergoing anticoagulation therapy for acute venous or arterial thrombosis at our medical center.

Methods: Patients were retrospectively identified from July 1998 to December 1998. Data collected included initiation and maintenance doses of heparin, frequency of monitoring and dose adjustments, time to the therapeutic range, complications and interruptions of therapy, and characteristics of heparin-to-warfarin transition.

Results: Of the 311 patients who met the study criteria during the 6-month period, 134 had venous thromboembolism, 122 had cerebral arterial thrombosis, and 55 had peripheral arterial thrombosis. Groups differed in use and magnitude of initial heparin bolus, frequency of monitoring, and time to the therapeutic range. Dose response to intravenous heparin was highly variable. Even when the activated partial thromboplastin time reached the therapeutic range of 55 to 85 seconds, the next 2 consecutive measurements remained in this range in only 29% of the patients. Patients received an average of 4 different heparin doses over the first 3 days of treatment, and the therapeutic range was maintained on each of 4 sequential days in only 7% of them. During the course of therapy, 54% of the patients had at least 1 prolonged interruption in heparin infusion, and 4.8% sustained a major hemorrhage. Overall, 20% of the patients met the currently recommended treatment guideline of 4 days or more of heparin and warfarin overlap, until the international normalized ratio is greater than 2.0 for 2 consecutive days.

Conclusions: Multiple challenges to effective anticoagulation treatment with unfractionated heparin exist in the hospital setting. Strategies are needed to improve the overall quality of anticoagulant care, including the substitution of low-molecular-weight heparin for unfractionated heparin, where appropriate.

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age also have an impact on the provision of hospital care. In the early phase of care, interval monitoring is challenged by diagnostic testing, which often causes patients to miss critically timed tests during heparin initiation. Optionally timed blood tests are further compromised by delays in patient transport and declining nurse-patient ratios. Moreover, pressures to reduce length of stay challenge the intensive use of hospital days that the drug overlap necessary in the transition of unfractionated heparin to warfarin entails.

In the face of such obstacles to high-quality use of unfractionated heparin, we sought to assess the real-world course of acute anticoagulation treatment among hospitalized patients treated for acute venous or arterial thrombosis at our academic medical center.

**METHODS**

**IDENTIFICATION OF STUDY PATIENTS**

Hospitalized patients treated with both unfractionated heparin and warfarin were identified from July 1998 to December 1998 using hospital laboratory and billing databases. Of 707 patients who had at least 2 aPTT measurements greater than 40 seconds and who were billed at least once for warfarin therapy, 335 (48%) were treated for acute thrombosis. The remaining 365 patients received unfractionated heparin and warfarin for prophylaxis of thromboembolism.

To be eligible for the study, patients needed to be 18 years or older and to have been treated with unfractionated heparin and warfarin for acute thrombosis or thromboembolism. All patients had indications for long-term warfarin therapy, which permitted evaluation of the transition from unfractionated heparin to warfarin. Patients treated with unfractionated heparin only, eg, those having acute coronary syndrome, were not eligible. Study patients were grouped by indication (cerebral or peripheral arterial thromboembolism, or venous thromboembolism), and by clinical service. Patients with an arterial thrombus, whether cerebral or peripheral, were treated nearly exclusively by the neurology or vascular surgery services. Medical records for 316 (94%) of the 335 patients with acute thromboembolism were available for detailed chart review. Of these 316 patients, 5 with a prior history of heparin-induced thrombocytopenia were excluded.

**SOURCE OF DATA**

Measurements for aPTT and international normalized ratios (INRs) were obtained from the hematology laboratory database. Demographic data and other clinical variables were extracted from the inpatient medical records. Doses of unfractionated heparin and warfarin were determined from physician orders and verified in the nursing medication sheets. During the study period, the medical service used a weight-based dosing nomogram for the initiation of unfractionated heparin (bolus, 80 U/kg; infusion, 18 U/kg per hour). For all services, the continuous intravenous heparin infusion was adjusted per algorithm to achieve the therapeutic aPTT range of 55 to 85 seconds, with the lower limit defined as 1.5 times control. We defined an interruption in unfractionated heparin therapy as temporary cessation of continuous heparin infusion for reasons other than an elevated aPTT or an uncomplicated change of indwelling venous catheter. Interruptions were documented in the daily progress notes or as a physician’s order to hold heparin.

**DESCRIPTIONS OF ANTICOAGULATION THERAPY AND QUALITY MEASUREMENTS**

Variables measured included initiating bolus and infusion doses of unfractionated heparin; number of patients in whom the lower limit of the therapeutic range was reached by the first aPTT measurement or by the end of the first calendar day; the number of aPTT measurements in the first 2 calendar days of heparin therapy; the number of heparin dose adjustments and additional bolus doses required in the first 3 calendar days of therapy; the number and type of interruptions in heparin infusion; the number of days of overlap of unfractionated heparin and warfarin therapies; and INRs at the times of heparin cessation, hospital discharge, and first outpatient follow-up appointment. Reviewing initial heparin bolus doses excluded 26 patients who were found to be already treated with unfractionated heparin when they were transferred to our hospital. Analyses involving the overlap of unfractionated heparin and warfarin therapies were limited to the 290 patients who completed their unfractionated heparin course prior to discharge.

**COMPLICATIONS OF ANTICOAGULANT THERAPY**

Major hemorrhage was defined as fatal, intracranial, retroperitoneal, or requiring transfusion of at least 2 U of packed red blood cells. Type 2 heparin-induced thrombocytopenia was defined by the presence of the anti-heparin platelet factor IV antibody using an enzyme immunoassay (Asserachrom HPIA; Diagnostica Stago, Asnières, France).

**STATISTICAL ANALYSES**

Comparisons of proportions were assessed with the Pearson χ² test. Group differences in heparin doses, number of days of heparin therapy, and number of interruptions in therapy were tested using nonparametric methods (Wilcoxon and Kruskal-Wallis rank-sum tests). The Bartlett test of equality of variance was used to compare the distributions of successive aPTT measurements. The Kaplan-Meier method was used to estimate the time to reach the lower limit of the therapeutic range as predicted by the number of aPTT measurements within the first 2 days of heparin therapy.

The study protocol was approved by the institutional review board of Massachusetts General Hospital.

**RESULTS**

During the 6-month study period, 311 patients were identified as having had an acute thrombosis treated with unfractionated heparin transitioned to warfarin therapy. The mean age was 65 years (range, 18-97 years) and 161 (52%) were women; 134 (43%) were treated for venous thromboembolism, 122 (39%) for a cerebrovascular event, and 55 (18%) for peripheral arterial thrombosis. Of the 134 patients with venous thromboembolism, 41 (31%) were treated for a pulmonary embolus and 58 (43%) had an active malignancy (Table 1).

**INITIATION OF UNFRACTIONATED HEPARIN**

Initiation of anticoagulant therapy with full-dose unfractionated heparin varied across indications (Table 2). More medical patients treated for venous thromboembolism received an initial bolus of heparin, and received higher bolus doses and higher infusion doses of unfractionated heparin, than patients in the other groups. In
these patients, the lower limit of the therapeutic range was more likely to be reached at the first aPTT measurement; however, it was also more likely to exceed 100 seconds, although this finding was not statistically significant. By the end of the first calendar day of intravenous heparin therapy, an aPTT of 55 seconds or greater was reached in 84% of patients with venous thromboembolism hospitalized on the medical service, compared with 50% on the surgery service. Patients treated for a cerebrovascular event or for peripheral arterial thrombosis had intermediate results. By the end of the second calendar day, the lower limit of the therapeutic aPTT range was not reached in 12% of the 311 patients.

STABILITY OF DOSE RESPONSE TO HEPARIN AND INTENSITY OF aPTT MONITORING

Dose response to heparin was highly variable across study patients. Even when the therapeutic aPTT range of 55 to 85 seconds was reached, it was maintained in the next 2 measurements in only 29% of patients. Compared with the range distribution of the first aPTT within this range, or index, the variance of the next consecutive aPTT measurements was significantly greater (P<.001) (Figure 1). During the first 3 calendar days of intravenous heparin therapy, 61% of patients received at least 4 different heparin infusion doses and 42% required additional intravenous bolus doses of heparin. The number of different heparin infusion doses over the first 3 days of treatment did not differ across indications (Table 3). The magnitude of dose variation was also similar across groups. Although the lower limit of the therapeutic aPTT range was reached in a higher percentage of patients hospitalized on the medical service through a more consistent weight-based approach to heparin initiation, the precision of heparin dosing was not increased and the frequency of subsequent dose adjustments was not reduced. Overall, 284 of the 311 patients who were given initiating therapy received unfractionated heparin for at least 4 days, and only 20 (7%) of these 284 patients had at least 1 aPTT measurement in the therapeutic range of 55 to 85 seconds each of the 4 sequential days.

During the first 2 calendar days of therapy, 55% of patients treated for venous thromboembolism on the medical service and 57% of patients treated for a cerebrovascular event on the neurology service had 5 or more aPTT measurements, compared with 38% of patients treated for venous thromboembolism on the surgery service. Frequent aPTT monitoring during the first 2 days was associated with a greater likelihood of reaching the lower limit of the therapeutic range (P=.002) (Figure 2).

COMPLICATIONS OF INTRAVENOUS HEPARIN THERAPY

The overall rate of major hemorrhage for patients receiving unfractionated heparin was 4.8% (n=15). Two hemorrhages were fatal, an intracranial hemorrhage 9 days after meningioma resection and a hemorrhage in a patient with ovarian cancer and disseminated intravascular coagulation. Seven of the 15 nonfatal hemorrhages occurred within the first 3 days of intravenous heparin therapy; 9 were spontaneous, and 6 were postprocedure

### Table 1. Clinical Characteristics of 311 Patients With Arterial or Venous Thrombosis

<table>
<thead>
<tr>
<th>Characteristic (n)</th>
<th>No. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Venous thromboembolism (134)</td>
<td>86</td>
</tr>
<tr>
<td>Medical patients</td>
<td>57</td>
</tr>
<tr>
<td>Pulmonary embolus</td>
<td>29</td>
</tr>
<tr>
<td>Surgical patients (48)</td>
<td>36</td>
</tr>
<tr>
<td>Deep venous thrombosis</td>
<td>12</td>
</tr>
<tr>
<td>Pulmonary embolus</td>
<td>79</td>
</tr>
<tr>
<td>Medical inpatient</td>
<td>9</td>
</tr>
<tr>
<td>Postoperative surgical inpatient</td>
<td>22</td>
</tr>
<tr>
<td>Surgical postoperative readmission</td>
<td>24</td>
</tr>
<tr>
<td>Active malignancy</td>
<td>58</td>
</tr>
<tr>
<td>Cerebrovascular event (122)</td>
<td>107</td>
</tr>
<tr>
<td>Stroke</td>
<td>12</td>
</tr>
<tr>
<td>Transient ischemic attack</td>
<td>4</td>
</tr>
<tr>
<td>Venous sinus thrombosis</td>
<td>31</td>
</tr>
<tr>
<td>Peripheral arterial thrombosis (55)</td>
<td>62</td>
</tr>
</tbody>
</table>

### Table 2. Initiation of Intravenous Heparin for Treatment of Thrombosis Across Indications

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Medical (n = 86)</th>
<th>Surgical (n = 48)</th>
<th>Cerebral (n = 122)</th>
<th>Peripheral (n = 55)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initiating bolus, %*</td>
<td>83</td>
<td>71</td>
<td>31</td>
<td>44</td>
<td>.001</td>
</tr>
<tr>
<td>Bolus dose, U/kg, median (IQR)†</td>
<td>73 (65-82)</td>
<td>66 (43-80)§</td>
<td>37 (22-55)</td>
<td>62 (51-68)</td>
<td>.001</td>
</tr>
<tr>
<td>Initial infusion, median (IQR)‡</td>
<td>15 (12-17)</td>
<td>14 (10-17)</td>
<td>13 (11-16)</td>
<td>13 (10-16)</td>
<td>.02</td>
</tr>
<tr>
<td>First aPTT &gt;=55 s, %</td>
<td>69</td>
<td>38¶</td>
<td>51</td>
<td>62</td>
<td>.003</td>
</tr>
<tr>
<td>First aPTT &gt;100 s, %</td>
<td>30</td>
<td>19</td>
<td>18</td>
<td>25</td>
<td>.18</td>
</tr>
<tr>
<td>aPTT &gt;=55 s on 1st day, %</td>
<td>84</td>
<td>50¶</td>
<td>68</td>
<td>71</td>
<td>.001</td>
</tr>
</tbody>
</table>

Abbreviation: aPTT, activated partial thromboplastin time; IQR, interquartile range.
*Excludes 26 patients with thromboembolism already administered heparin when transferred: 3 cases of venous, 16 cases of cerebrovascular, and 7 cases of peripheral arterial thromboembolism.
†Excludes 10 patients with weight record missing: 8 cases of venous, 1 case of cerebrovascular, and 1 case of peripheral arterial thromboembolism.
‡Excludes 17 of 311 patients with weight record missing: 9 cases of venous and 8 cases of cerebrovascular thromboembolism.
§Medical venous thromboembolism group vs surgical venous thromboembolism group, P<.05.
¶Medical venous thromboembolism group vs surgical venous thromboembolism group, P<.001.
complications. The mean aPTT at the time of hemorrhage was 109 seconds among the 14 patients with an aPTT result available, and greater than 85 seconds in 11 of them. The mean infusion dose of heparin at the time of hemorrhage was 15 U/kg per hour, and the mean cumulative heparin dose over the preceding 24 hours was 25800 U. Following cessation of bleeding and stabilization, 9 patients were eventually discharged with warfarin therapy. The surgery and neurology services experienced higher rates of major hemorrhage, 8% and 7% respectively, but these rates were not significantly different from those of patients being treated on the medical service for venous thromboembolism ($P = .19$) (Table 4). Of the 311 patients who received initiating intravenous heparin therapy, 9 (2.9%) developed heparin-induced thrombocytopenia and 4 of them had completed the course of their heparin therapy at the time of diagnosis.

**INTERRUPTION OF INTRAVENOUS HEPARIN THERAPY**

To better assess the course of heparin therapy among hospitalized patients, we also studied the frequency of temporary interruptions in heparin infusion. There were 265 interruptions among 169 (54.3%) patients, and 71 of them had 2 or more interruptions in heparin delivery. Forty-eight percent of these disruptions were linked with the infusion hardware (eg, its incompatibility with magnetic resonance imaging equipment), and a few were due to difficulties with intravenous access. Invasive procedures or major surgery were the cause of 42% of the interruptions. The rates and distribution of causes for interruption differed across indications and clinical services (Table 4).

**HEPARIN-TO-WARFARIN TRANSITION**

Of the 311 patients who underwent intravenous heparin initiation, 291 (93.6%) continued to receive the treatment. Heparin was discontinued in 20 patients (6 because of major hemorrhage, 5 because of heparin-induced thrombocytopenia, 4 because of in-hospital deaths unrelated to anticoagulant therapy, and 5 because the patients were not thought to be safe long-term anticoagulation candidates). Of the 291 patients who continued to receive heparin therapy, 41 completed the course after their hospital discharge (16 were transferred to rehabilitation facilities while taking intravenous heparin and 25 were transitioned to low-molecular-weight heparin). Analyses of the overlap of unfractionated heparin and warfarin therapies were limited to the 250 patients who completed their heparin course prior to hospital discharge.

The overlap of heparin and warfarin therapies was less than 4 days in 41% of the patients hospitalized with venous thromboembolism on the surgery service, and in 32% of those with a cerebrovascular event on the neurology service, compared with 19% of those with venous-
of the aPTT was essential to reaching the therapeutic range.

The risk-benefit ratio of aggressive anticoagulation treatment among different subsets of patients needs further study. In our study, patients treated for a cerebral or peripheral arterial thrombosis were much less likely than those treated for venous thrombosis to have unfractionated heparin therapy initiated with a bolus dose (31% and 44%, respectively). Patients hospitalized on the surgery or neurology service had a higher rate of major hemorrhage (6.2% overall, and 3.1% within the first 3 days of therapy). Although these rates were not statistically different from rates on the medical service, they may be a reflection of the small number of patients rather than a true assessment of bleeding risk.

The pharmacokinetic limitations of unfractionated heparin have been studied extensively. Its nonspecific binding to plasma proteins interferes with its anticoagu-
lant effect, especially among patients with elevated levels of acute-phase reactants and procoagulants, eg, those with thromboembolic disorders, malignancy, or who underwent major surgery. In our study, even after an aPTT therapeutic range of 55 to 85 seconds was reached, the next 2 consecutive aPTT measurements remained in this range in only 29% of patients. We also found that, although a weight-based approach to initiate unfractionated heparin resulted in a greater likelihood of achieving the lower limit of the therapeutic range, it also more often resulted in an aPTT greater than 100 seconds. Furthermore, a weight-based approach did not decrease the need for later dose adjustment. At least 1 aPTT measurement remained in the therapeutic range of 55 to 85 seconds on each of 4 sequential days of therapy in only 7% of patients. These findings emphasize the importance of frequent monitoring even after achieving the target range when using unfractionated heparin.

The realities of hospital care for acutely ill patients make optimal monitoring of heparin therapy difficult. Fifty-four percent of patients had at least 1 prolonged interruption in heparin infusion and 23% had 2 or more. This fragmentation of drug delivery causes erratic anticoagulant treatment and control, stemming from inappropriately timed testing in relation to drug reinitiation. These real-world challenges decrease the effectiveness of unfractionated heparin therapy and may partly explain the difficulty of achieving and maintaining the therapeutic range. Where appropriate and feasible, increased plain the difficulty of achieving and maintaining the therapeutic range. Where appropriate and feasible, increased plain the difficulty of achieving and maintaining the therapeutic range. Where appropriate and feasible, increased plain the difficulty of achieving and maintaining the therapeutic range. Where appropriate and feasible, increased plain the difficulty of achieving and maintaining the therapeutic range. Where appropriate and feasible, increased plain the difficulty of achieving and maintaining the therapeutic range. Where appropriate and feasible, increased plain the difficulty of achieving and maintaining the therapeutic range. Where appropriate and feasible, increased plain the difficulty of achieving and maintaining the therapeutic range. Where appropriate and feasible, increased plain the difficulty of achieving and maintaining the therapeutic range. Where appropriate and feasible, increased plain the difficulty of achieving and maintaining the therapeutic range. Where appropriate and feasible, increased plain the difficulty of achieving and maintaining the therapeutic range. Where appropriate and feasible, increased plain the difficulty of achieving and maintaining the therapeutic range. Where appropriate and feasible, increased plain the difficulty of achieving and maintaining the therapeutic range. Where appropriate and feasible, increased plain the difficulty of achieving and maintaining the therapeutic range. Where appropriate and feasible, increased plain the difficulty of achieving and maintaining the therapeutic range. Where appropriate and feasible, increased plain the difficulty of achieving and maintaining the therapeutic range. Where appropriate and feasible, increased plain the difficulty of achieving and maintaining the therapeutic range. Where appropriate and feasible, increased plain the difficulty of achieving and maintaining the therapeutic range. Where appropriate and feasible, increased plain the difficulty of achieving and maintaining the therapeutic range. Where appropriate and feasible, increased plain the difficulty of achieving and maintaining the therapeutic range. Where appropriate and feasible, increased plain the difficulty of achieving and maintaining the therapeutic range. Where appropriate and feasible, increased plain the difficulty of achieving and maintaining the therapeutic range. Where appropriate and feasible, increased

Given the appropriate outpatient structure, transition to low-molecular-weight heparin may allow earlier discharge among selected patients, resulting in a more assured transition to warfarin therapy.

The purpose of this study was to assess the real-world experience of in-hospital management of acute thromboembolism with unfractionated heparin at our medical center. The adequacy of anticoagulant effect, the timeliness of achieving that effect, the frequency of aPTT monitoring, the overlap of heparin and warfarin, and the adequacy of anticoagulation therapy at the time of discharge are all measurable parameters that are relevant and central to the treatment of both arterial and venous thrombotic disease. Because our study focused on acute in-hospital care, we did not follow up patients after discharge. We are therefore unable to provide longer-term outcomes, which is a limitation of our study.

In this study, we attempted to characterize the challenges to realizing anticoagulation goals among a cohort of patients hospitalized with medically complex conditions. The intensity of care surrounding monitoring and maintenance of infusion, the extended use of hospital days, and the frequency of therapy interruptions all have important implications for the quality and cost of the treatment of thrombotic disease.

CONCLUSIONS

Acute management of thrombotic disease remains suboptimal in real-world practice. In our study, few patients actually met the currently recommended anticoagulation therapy guidelines for conversion of unfractionated heparin to warfarin. Strategies are needed to improve the overall quality of anticoagulant care in the inpatient setting, including expanding the use, where appropriate, of low-molecular-weight heparin.

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REFERENCES


4. Flaker GC, Bartolozzi J, Davis V, et al. Use of a standardized heparin nomogram

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