Use of a Heparin Nomogram for Treatment of Patients with Venous Thromboembolism in a Community Hospital

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Summary

Background: The application of a heparin dosing nomogram in the treatment of patients with venous thromboembolism resulted in improvement of heparin therapy in clinical research settings. In 1992 a heparin nomogram was introduced in our hospital, which is a community hospital where anticoagulant therapy is supervised by the attending physicians. We studied whether comparable improvements were achieved in such a non-surveyed clinical setting. Methods: Patients were identified from computerized discharge records, and classified into a pre-nomogram (discharged in 1990 or 1991) and a nomogram patient group (discharged in 1993 or 1994). The use of the nomogram was encouraged but the application remained on a voluntary basis. Since the definition of the target APTT range was different in the pre-nomogram period as compared to the nomogram period, a formal analysis of pre- and post-nomogram results was not considered justified. Results: The APTT ratio, six hours after the start of heparin treatment, was below the predefined lower limit in 72% of 127 patients in the pre-nomogram group and in 13% of 127 patients in the nomogram group. During 1043 days heparin therapy in the nomogram group the morning APTT ratio was subtherapeutic in 8%. In 58% of all APTT results the physician responded according to the nomogram. The subsequent APTT was in the target range in 64% of the cases compared to 31% if the adjustment was not performed according to the nomogram (P<.0001). Major bleeding episodes occurred in 3.1% in the pre-nomogram period and in 0.7% in the nomogram period.

Conclusion: The present study shows that the introduction of a heparin dosing nomogram in a non-research clinical setting results in more adequate heparin anticoagulation with low risks of bleeding.

Introduction

Initial adjusted dose heparin therapy in patients with established venous thromboembolism (VTE) requires rapid achievement and maintenance of a therapeutic activated partial thromboplastin time (APTT) test result in order to prevent recurrent VTE on the one hand, and to avoid an excessively prolonged APTT to minimize the risk of major bleeding on the other hand. For these reasons, at least daily monitoring of heparin treatment is mandatory. The APTT target range is usually defined as a ratio between 1.5 and 2.5 times the control APTT value using a thromboplastin reagent. This range corresponds to a heparin level of 0.2-0.4 U/ml by protamine titration assay which is generally considered to be the therapeutic range for the treatment of patients with VTE (1, 2).

A series of clinical studies have documented that the usual monitoring of heparin dosing often fails in achieving the defined goals (3, 4). This has led to the design of nomograms for initial dosing of heparin and subsequent dose adjustments, which have shown to improve heparin therapy. However, these observations were made in clinical research settings (5-8).

In 1992 a heparin nomogram was introduced in our hospital, which is a community hospital where anticoagulant therapy is supervised by the attending physicians. The use of the nomogram was encouraged but the application remained on a voluntarily basis. To determine the adequacy of this approach, in a non-surveyed clinical setting, we retrospectively analysed the quality of heparin treatment in all patients with venous thromboembolism (VTE) throughout 1993 and 1994. Heparin treatment in the 1991 and 1992 pre-nomogram period served as a reference. Since the definition of the target APTT range was different in the pre-nomogram period as compared to the nomogram period, a formal analysis of pre- and post-nomogram results was not considered justified.

Methods

Patients

All patients with a discharge diagnosis of VTE, confirmed by objective diagnostic techniques, were eligible for the study. Patients were identified from computerized discharge records, and classified into a pre-nomogram (discharged in 1990 or 1991) and a nomogram patient group (discharged in 1993 or 1994). Patients were excluded if they were either not treated with intravenous heparin or received thrombolytic therapy.

Study Design

In the pre-nomogram period heparin therapy was initiated with 5000 IU i.v. heparin bolus and a subsequent continuous infusion rate determined by the attending physician. The dose of intravenous heparin therapy was adjusted by the attending physician, based on the patient’s APTT response. The APTT method used, a commercial reagent with kaolin activator (Boehringer, Germany) and manual endpoint detection, had a normal range of 25-37 sec and the recommended target range was 60-85 sec. If required, the heparin dose-adjustments consisted of increasing or decreasing the maintenance infusion rate with 5000 IU heparin per 24 h. In September 1992 a heparin nomogram was introduced, including a weight-based bolus, a weight-based initial continuous infusion rate, and subsequent dose adjustments, which have shown to improve heparin therapy. However, these observations were made in clinical research settings (5-8).

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All information was extracted from medical charts and nursing notes by a single investigator, using a priori specified criteria for adequacy of heparin response. Specific attention was given to episodes of clinically relevant bleeding, including a search for the indication to interrupt heparin treatment or to decrease the administration rate for reasons other than provided by the nomogram. In addition changes in the hemoglobin levels were recorded. Major bleeding episodes were documented addressing the complete hospitalisation period. Major bleeding was defined as clinically overt and associated with a decrease in hemoglobin level of at least 1.3 mmol/l or accompanied by transfusion of packed red blood cells or by the cessation of heparin therapy. Clinical causes of death were documented and autopsy study results if available were included.

Results

Patient Characteristics

A total of 355 consecutive patients were identified with a discharge diagnosis of VTE, 173 patients in the pre-nomogram period and 182 in the nomogram period. A total of 75 (21%) patients were excluded for the following reasons: 40 Patients died without a previous clinical suspicion of VTE. In 25 of these patients the diagnosis of VTE was revealed at autopsy, and in the remaining 15 patients the diagnosis was based on clinical symptoms at the time of death. Twenty patients received thrombolytic therapy, low molecular weight heparin, oral anticoagulants only or no treatment. The remaining 15 patients were excluded because missing information precluded adequate evaluation. Therefore, 280 patients were available for analysis, 127 in the pre-nomogram period and 153 in the nomogram period. In 26 of the 153 patients in the nomogram group heparin treatment was initiated before a pre-treatment APTT was obtained. This excluded the use of the nomogram and therefore the dose adjustments made in this group are analyzed separately. The patient characteristics of these 26 patients are comparable to the remaining 127 patients in the nomogram group. The baseline characteristics of the study groups are summarized in Table 2.

Table 1  Heparin dosing nomogram

<table>
<thead>
<tr>
<th>Loading dose:</th>
<th>&lt; 50 kg: 3500 IU</th>
<th>50–90 kg: 5000 IU</th>
<th>&gt; 90 kg: 7500 IU</th>
</tr>
</thead>
</table>

Initial maintenance infusion:
2.1 ml/h = 1260 IU/h = 30240 IU/24 h for a 80 kg body weight.
For each 5 kg increase/decrease in weight, adjust ± 0.1 ml

Maintenance infusion adjustment:
Measure APTT ratio 6 h after initiating the maintenance infusion and adjust as follows

<table>
<thead>
<tr>
<th>ratio</th>
<th>bolus IU</th>
<th>stop min</th>
<th>rate change ml/h</th>
<th>repeated APTT h</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 1.2</td>
<td>5000</td>
<td>0</td>
<td>+0.3</td>
<td>6</td>
</tr>
<tr>
<td>&lt; 1.5</td>
<td>5000</td>
<td>0</td>
<td>+0.2</td>
<td>6</td>
</tr>
<tr>
<td>1.5–2.5</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>Next AM</td>
</tr>
<tr>
<td>2.5–3.0</td>
<td>0</td>
<td>0</td>
<td>−0.2</td>
<td>Next AM</td>
</tr>
<tr>
<td>3.0–3.7</td>
<td>0</td>
<td>30</td>
<td>−0.2</td>
<td>6</td>
</tr>
<tr>
<td>&gt; 3.7</td>
<td>0</td>
<td>60</td>
<td>−0.3</td>
<td>6</td>
</tr>
</tbody>
</table>

Table 2  Patient characteristics

<table>
<thead>
<tr>
<th></th>
<th>pre-nomogram</th>
<th>nomogram</th>
<th>pre-treatment APTT</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>yes</td>
<td>no</td>
<td>yes</td>
</tr>
<tr>
<td>Number of patients</td>
<td>127</td>
<td>26</td>
<td>127</td>
</tr>
<tr>
<td>mean age, y ± 1 SD</td>
<td>63 ± 17</td>
<td>62 ± 18</td>
<td>72 ± 13</td>
</tr>
<tr>
<td>weight, kg ± 1 SD</td>
<td>N. A.</td>
<td>78 ± 14</td>
<td>73 ± 14</td>
</tr>
<tr>
<td>men, %</td>
<td>35</td>
<td>47</td>
<td>63</td>
</tr>
<tr>
<td>primary PE %</td>
<td>87</td>
<td>71</td>
<td>92</td>
</tr>
<tr>
<td>PE with concomitant DVT %</td>
<td>13</td>
<td>29</td>
<td>8</td>
</tr>
</tbody>
</table>

Risk factors

<p>| | | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
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</tr>
</thead>
<tbody>
<tr>
<td>neoplasm, %</td>
<td>25</td>
<td>21</td>
</tr>
<tr>
<td>postoperative, %</td>
<td>12</td>
<td>8</td>
</tr>
<tr>
<td>previous thromboembolism, %</td>
<td>6</td>
<td>11</td>
</tr>
</tbody>
</table>

1 N. A. = not applicable; 2 PE = Pulmonary Embolism; 3 DVT = Deep Vein Thrombosis

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In the pre-nomogram period 65% (631) of all APTT test results (971) were outside the target range. In 51% of these situations no adjustments were made, whereas when a dose adjustment was made this resulted in a subsequent APTT within the target range in 32% of these cases. Fig. 2 shows the distribution of morning APTT ratio’s during the first 7 days in the nomogram group. Subtherapeutic APTT’s (ratio below 1.5) and excessively prolonged APTT’s (ratio above 3.7) were revealed in a minority of the APTT results. In 58% of all APTT results the physician responded according to the nomogram. The subsequent APTT was in the target range in 64% of the cases compared to 31% if the adjustment was not performed according to the nomogram (P < .0001).

An excessively prolonged APTT ratio (>3.7) was measured at least once on 7% of all heparin treatment days in the nomogram group, compared with an APTT of more than 120 sec (corresponding to a similar ratio) in 17% in the pre-nomogram group.

**Major Bleeding and Death**

The rates of clinically significant bleeding and death were studied in all pre-nomogram and nomogram patients (including the 26 patients without a pre-treatment APTT) covering the complete hospital stay. In the pre-nomogram group 4 (3.1%) (95% CI 0.1-6.2%) major bleeding episodes occurred in 127 patients with a fatal outcome in 1 patient, versus 1 (0.7%) (95% CI 0.0-2.6%) non-fatal bleeding episode in 153 patients during the nomogram period (Table 3). Only one patient (no. 2, Table 3) had an excessively prolonged APTT (185 sec). In the nomogram group, a severely prolonged INR prior to the bleeding episode seems predominantly responsible for the bleeding tendency of the patient (no. 5).

Death during hospital stay occurred in 20 patients, 14 patients in the pre-nomogram and 6 patients in the nomogram group. Autopsy revealed massive pulmonary embolism in 2 patients in the pre-nomogram group and in 2 patients in the nomogram period. In 3 of 11 patients in the pre-nomogram group without autopsy and in 2 out of 4 patients without autopsy in the nomogram period, progression of pulmonary embolism was considered the cause of death according to the physician in charge of those patients.

**Discussion**

This study shows that in the period before the introduction of the nomogram, heparin dosing was frequently inadequate. The introduction of the nomogram in 1992 resulted in several changes in heparin management which could account for the satisfactory results in achieving and maintaining therapeutic anticoagulation.

First, a standard heparin intravenous solution concentration of 60 IU/0.1 ml, made by the pharmacist, was used. In the pre-nomogram period a new 24 hour solution was made by the nurse each time a change in heparin dose was ordered. This may have increased the risk of incorrect dosing.

Second, the suggested heparin bolus and initial maintenance infusion rate were body weight adjusted. This resulted in an average increase of the maintenance infusion dose from 24070 (± 3576) in the pre-nomogram period to 28.800 (± 2800) U/24 h in the nomogram period. As a result only 13% of patients in the nomogram period had a subtherapeutic APTT response 6 hours after initiation of heparin therapy, without an increase in excessively prolonged APTT’s.

Third, the nomogram advised infusion rate changes based on the obtained APTT ratio’s, instead of empiric dosing by the individual physician. Although low rates of both insufficiently prolonged APTT ratio’s and excessively prolonged APTT ratio’s were accomplished (Fig. 2), a
trend towards higher APTT ratio’s is observed in the first 5 to 7 days of heparin therapy. This trend can be a result of a substantial percentage (42%) of responses performed not according to the nomogram with a consequently lower succes rate (33% instead of 64%) or insufficient decreases of maintenance infusion in the nomogram. The majority of rate adjustments not done according to the nomogram were performed by a subgroup of senior and experienced physicians. These physicians had the impression that consultation of the nomogram was not necessary for them to achieve the therapeutic goals. It is obvious that the results of this study can be used to improve adherence to the nomogram.

APTT results are surrogate end-points in evaluating safety and efficacy of heparin therapy in VTE. Because we did not measure heparin levels by protamine sulfate titration we cannot be sure that all patients having an adequate APTT ratio had indeed a minimum heparin level of 0.2 U/ml. Clinically relevant bleeding episodes were infrequent (Table 3) both before introduction of the nomogram (3.1%) and during the use of the nomogram (0.7%). Because the comparability of bleeding risks in both groups was not determined we are not allowed to analyse statistically this difference in bleeding rate. Autopsy revealed 2 patients in each study period with massive pulmonary embolism. For lack of sufficient number of autopsies, data considering the cause of death remain undetermined in many cases. The determination of the recurrence rate of VTE after the initial hospitalisation period was not addressed in this study.

Although the importance of exceeding the lower limit of the target range within 24-48 h has been strongly emphasized in order to prevent recurrent VTE (1, 6, 9), a recent review could not confirm this association (10). For this review, studies were eligible only if the starting infusion rate of heparin was at least 30,000 IU per 24 h, which clearly results in a lower number of patients with initial subtherapeutic APTT’s compared to the previously recommended starting dose of 25,000 IU per 24 h. Other studies have evaluated even higher starting doses (40,000 IU per 24 h) in patients without an identifiable risk factor for bleeding, based on the concept that the risk of hemorrhage is not linearly correlated with increasingly prolonged APTT’s. This resulted in a low number (10-15%) of patients with an initial subtherapeutic APTT without an increase in bleeding (2 major bleedings in totally 82 treated patients) (5, 8). However frequent APTT monitoring is required when employing such a high starting dose. This is probably feasible in the course of a clinical trial but it remains to be determined if a similarly low bleeding rate can be accomplished in a day to day clinical setting.

The well known limitations of a retrospective study also apply to our study. However, the fact that there was no ongoing prospective study analysing the effects of the introduction of the nomogram may also have had an advantage. It might have resulted in a better understanding of how physicians respond to the introduction of a nomogram in a non-surveyed clinical setting.

Our results in the nomogram period showed that both, the time needed to exceed the therapeutic threshold (Fig. 1) and the observed rates of APTT’s outside the target range (Fig. 2), are fully comparable with the results found in the research studies (5-8). The application of a heparin nomogram has previously been studied in two community hospitals (11, 12). The results of Hollingsworth et al. (11) were clearly less favourable than those derived from the clinical research settings (5-8).

In fact, only 30% of the patients reached a therapeutic APTT result after 24 hours heparin therapy which increased to 60% after 48 hours, compared with 68%-90% and 90%-100% respectively in the research studies (5-8). Raschke et al. (12) described the effective implementation of a nomogram after having performed a randomized trial (6) at their institution. Familiarity with the nomogram could have had a positive effect on clinicians willingness to use the nomogram. Furthermore, both previously described community hospital studies (11, 12) differed from our study by excluding patients if VTE was coded as a secondary diagnosis.

The present study shows that the introduction of a heparin dosing nomogram in clinical practice in a non-monitored research setting results in more adequate heparin anticoagulation and low bleeding rates comparable with results from clinical trials (5-8).

References


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