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CHAPTE RR  5

NOMOGRAMS FOR THE ADMINISTRATION OF UNFRACTIONATED HEPARIN IN THE INITIAL TREATMENT OF ACUTE THROMBOEMBOLISM AN OVERVIEW


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Summary

Despite the availability of low-molecular-weight heparins, unfractionated heparin (UFH) still remains the drug of choice for the initial treatment of acute venous thromboembolism in many countries. When appropriately employed, UFH treatment results in a degree of efficacy and safety that is fully comparable with that obtained with the use of heparin derivatives. The use of nomograms for the intravenous or subcutaneous administration of UFH assures that virtually all patients will promptly achieve adequate levels of anticoagulation, thus decreasing the likelihood of recurrent venous thromboembolism without extra bleeding-risk.

In this article we reviewed clinical studies on the implementation and validation of UFH dosing nomograms, and attempted a quantitative analysis of their performance. According to the results of our analysis, a statistically significantly higher proportion of patients treated on the basis of a nomogram reached a therapeutic anticoagulant level within 24 hours of treatment, as compared to patients treated following the standard practice (odds ratio, 3.6; 95% CI, 2.6 to 4.9). The rate of recurrent thromboembolic events was significantly lower for patients treated according to a nomogram (odds ratio, 0.3; 95% CI, 0.1 to 0.8), while no significant differences in terms of either major or minor bleedings were detected between nomogram patients and controls.
Introduction

The use of unfractionated or low-molecular weight heparin in the initial treatment of acute venous and arterial thromboembolism is mandatory in order to reduce the risk of recurrent thromboembolic events.\(^1\)\(^2\) As the anticoagulant response to unfractionated heparin (UFH) varies among patients, its therapeutic administration must be monitored by means of laboratory tests, usually the activated partial thromboplastin time (aPTT).\(^3\) To obtain a fair balance between efficacy and safety, aPTT levels should be maintained within a predefined interval, either expressed as range (in seconds), or as a ratio (of the laboratory control aPTT).\(^2\)\(^3\) Obtaining a prompt and sustained anticoagulant level, however, is quite a difficult task to achieve.\(^5\) To this purpose, several standardised UFH administration strategies (nomograms) have been proposed to assure a timely achievement of therapeutic aPTT levels. This article reviews studies on the implementation and validation of UFH dosing nomograms, and attempts a quantitative analysis of the performance of different nomograms.

Methods

We searched Medline and Embase databases between 1980 and 1999, with the keywords “heparin”, “unfractionated”, “administration”, “nomogram”, and “protocol”. Additionally, we manually scanned the reference sections of identified studies and review articles to locate further relevant studies. Only full-text articles on the use of heparin nomograms were eligible for the analysis. The paper is arranged in two sections: a qualitative review of all retrieved papers on heparin dosing nomograms, and a quantitative review including only studies with a control population, made up of patients who were administered UFH on an empirical basis. The primary outcome for the quantitative analysis was the difference between the proportion of nomogram and control patients reaching an aPTT above the therapeutic threshold within 24 hours. The “therapeutic threshold” was defined as the lower limit of any given therapeutic range for aPTT. As secondary end-points we compared the efficacy and safety (as expressed by recurrent VTE and bleeding events, respectively) of heparin nomograms to empirical heparin administration. The secondary outcome analysis was confined to patients treated for venous thromboembolism (VTE). Differences across studies between either of the two strategies in terms of primary and secondary outcome were compared with Mantel-Haenszel technique. A statistical test for homogeneity was incorporated in the model.
Results

Overall, 16 studies were identified by searches. Of these studies, four were randomised trials, and the remaining 12 were prospective cohort studies with or without control patients. Nine studies reported on clinically relevant events, and VTE recurrence was objectively documented in five. In all studies but one, UFH was administered intravenously, and the initial UFH dosage was either given in fixed-dose or individually adjusted according to the patients' body weight.

Fixed-dose nomograms (Table 1)

Among the six identified studies, in three the same initial UFH dose was employed for all patients, and in the remaining three two different initial dosages were used according to the potential (high or low) patients' bleeding risk. In all of these studies, UFH was administered intravenously for the treatment of acute VTE. Four studies compared nomogram versus empirical UFH administration, and one compared two (aPTT-versus anti-Xa based) nomograms.

Overall, more than 60% of the patients treated on the basis of a nomogram achieved a therapeutic aPTT level within 24 hours from the beginning of heparin administration, the proportion being higher than 95% in two of the three trials in which patients were stratified according to the patients' bleeding risk. As compared to controls, a statistically significantly higher number of the nomogram patients reached a therapeutic aPTT within 24 hours. Furthermore, the mean time elapsed to obtain a therapeutic aPTT was significantly shorter. Patients treated on the basis of a nomogram were more likely to have overtherapeutic aPTTs, persisting for 24 hours or more in many instances, but bleeding events during heparin administration occurred with similar (low) frequency with both strategies.

Three out of the six studies that employed fixed doses of initial UFH reported on the clinical follow-up of the patients. In two studies, no significant differences in terms of recurrent or bleeding events were detected between nomogram and control patients, after an average follow-up of three months. In the third trial, recurrent and major bleeding events occurred with a comparable frequency to that reported in other similar studies.

A single trial compared the relative efficacy and safety of an anti-Xa nomogram to a fixed-dose nomogram in patients requiring large (>35,000 U/day) daily doses of heparin. Patients treated according to the anti-Xa nomogram had
Table 1 - Overview of fixed-dose nomograms

<table>
<thead>
<tr>
<th>Leading author</th>
<th>Patients *</th>
<th>n.</th>
<th>Bolus (U)</th>
<th>Initial dosage (U/h)</th>
<th>Target</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fennerty*</td>
<td>nr</td>
<td>54</td>
<td>5000</td>
<td>1400</td>
<td>1.5-2.5 (‡)</td>
</tr>
<tr>
<td>Cruickshank⁵</td>
<td>vte</td>
<td>50</td>
<td>5000</td>
<td>1280</td>
<td>60-85 sec</td>
</tr>
<tr>
<td>Hull⁰</td>
<td>vte</td>
<td>199</td>
<td>5000</td>
<td>1680 §</td>
<td>1.5-2.5 (‡)</td>
</tr>
<tr>
<td>Levine⁺¹¹</td>
<td>vte</td>
<td>126</td>
<td>5000</td>
<td>1400</td>
<td>60-85 sec</td>
</tr>
<tr>
<td>Elliott¹²</td>
<td>vte</td>
<td>20</td>
<td>5000</td>
<td>1680 §</td>
<td>55-85 sec</td>
</tr>
<tr>
<td>Hollingsworth¹⁵</td>
<td>vte</td>
<td>81</td>
<td>5000</td>
<td>1680 §</td>
<td>60-85 sec</td>
</tr>
</tbody>
</table>

nr: not reported; na: not applicable.
* vte: venous thromboembolism.
† DB&A: kaolin cefalin clotting time (Diogen, Bell, and Alton); Dade FS: Dade actin FS (Mississauga; Ontario); OA-aPTT: automated aPTT reagent (Organon Teknika Corp.; Durham, NC).

daily mean aPTT levels below the therapeutic range throughout the whole study, and were administered statistically significantly lower heparin amounts. However, no relevant differences in terms of efficacy and safety were detected between the two groups after an average follow-up of three months.

Weight-based nomograms (Table 2)

Among the ten identified studies; eight employed initial doses adjusted on a units per kilogram basis,⁷,¹¹,¹³,¹⁶-¹⁸,¹⁹,²¹ while two allocated patients to predefined weight categories.²⁰,²² Heparin was administered intravenously or subcutaneously for the treatment of both venous or arterial thromboembolism. Six studies compared nomogram-based versus empirical UFH administration,¹¹,¹₄,¹₇,¹₉,²⁰ two were cohort studies,¹₆,²² and the last compared a weight-based to a fixed-dose nomogram.²¹

Overall, more than 70 to 97 % of the patients treated on the basis of a weight-based nomogram achieved a therapeutic aPTT within 24 hours. A statistically significantly higher number of nomogram patients reached a therapeutic aPTT within 24 hours.¹¹,¹₄,¹₇,¹₉ Moreover, the mean time elapsed to obtain a therapeutic aPTT was significantly shorter.¹¹,¹₈,²⁰,²¹

Six studies that employed weight-adjusted initial UFH doses reported on the clinical outcome of the patients.¹¹,¹₄,¹₈,²₀,²₂ Among comparative studies, no signif-
Heparin

<table>
<thead>
<tr>
<th>Reagent †</th>
<th>n.</th>
<th>Bolus (U)</th>
<th>Initial dosage (U/h)</th>
<th>aPTT Target</th>
</tr>
</thead>
<tbody>
<tr>
<td>DB&amp;A</td>
<td>na</td>
<td>na</td>
<td>na</td>
<td>na</td>
</tr>
<tr>
<td>Dade FS</td>
<td>53</td>
<td>5000</td>
<td>1128</td>
<td>55-75 sec</td>
</tr>
<tr>
<td>Dade FS</td>
<td>na</td>
<td>na</td>
<td>na</td>
<td>na</td>
</tr>
<tr>
<td>Dade FS</td>
<td>na</td>
<td>na</td>
<td>na</td>
<td>na</td>
</tr>
<tr>
<td>OA-aPTT</td>
<td>48</td>
<td>5052</td>
<td>1041</td>
<td>55-85 sec</td>
</tr>
<tr>
<td>nr</td>
<td>82</td>
<td>5000</td>
<td>1147</td>
<td>60-85 sec</td>
</tr>
</tbody>
</table>

† Indicates aPTT ratio.
§ High bleeding risk patients received a lower starting dose (1240 U/h).
¶ Including patients requiring 35,000 U of heparin per day, who were randomised to monitoring either by aPTT or Anti-factor Xa levels.

Significant differences were reported between the nomogram and the control populations in terms of bleeding,\(^\text{11,14,18-20}\) whereas a sub-group analysis limited to patients with VTE showed a lower rate of recurrences in the nomogram group in one study.\(^\text{11}\)

Only one trial\(^\text{21}\) compared the relative efficacy and safety of a weight-based nomogram with a fixed-dose nomogram. Although the mean time required to exceed the therapeutic threshold was significantly shorter in patients treated with weight-adjusted UFH, no differences were observed between groups in terms of time required to reach the aPTT range, or proportion of patients exceeding the aPTT threshold within 24 hours.

**Quantitative analysis**

The results of the quantitative evaluation are reported in Table 3. Briefly, a statistically significant higher proportion of patients treated on the basis of a nomogram had an aPTT above the therapeutic threshold within 24 hours of treatment, as compared to control patients (odds ratio, 3.6; 95% CI, 2.6 to 4.9; p<0.0001). The frequency of recurrent VTE was statistically significantly lower for patients treated according to a nomogram (odds ratio 0.3; 95% CI, 0.1 to 0.8; p=0.001), while the relative figures for major and minor bleeding events were quite comparable.
Table 2 - Overview of weight-based nomograms

<table>
<thead>
<tr>
<th>Leading author</th>
<th>Patients *</th>
<th>n.</th>
<th>Bolus (U)</th>
<th>Initial dosage (U/h)</th>
<th>aPTT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Saya'</td>
<td>vte, af, cva</td>
<td>26</td>
<td>50 U/Kg</td>
<td>§</td>
<td>1.5-2.5 ¶</td>
</tr>
<tr>
<td>Raschke11,16</td>
<td>vte, aai, ua</td>
<td>63</td>
<td>80 U/Kg</td>
<td>18 U/Kg/h</td>
<td>46-70 sec</td>
</tr>
<tr>
<td>Rivey14</td>
<td>vte</td>
<td>42</td>
<td>70 U/Kg **</td>
<td>15 U/Kg/h</td>
<td>1.5-2.0 ¶</td>
</tr>
<tr>
<td>Kershaw††17</td>
<td>vte, ami</td>
<td>131</td>
<td>70 U/Kg ‡</td>
<td>13-16 U/Kg/h</td>
<td>1.5-2.5 ¶</td>
</tr>
<tr>
<td>Gunnarsson19</td>
<td>vte, ami, ua</td>
<td>45</td>
<td>75 U/Kg</td>
<td>13 U/Kg/h</td>
<td>55-95 sec</td>
</tr>
<tr>
<td>Brown18</td>
<td>vte, chd</td>
<td>28</td>
<td>80 U/Kg</td>
<td>18 U/Kg/h</td>
<td>60-85 sec</td>
</tr>
<tr>
<td>de Groot‡‡20</td>
<td>vte</td>
<td>127</td>
<td>3500-7500 U</td>
<td>-16 U/Kg/h</td>
<td>1.5-2.5 ¶</td>
</tr>
<tr>
<td>Prandoni§§¶¶22</td>
<td>vte</td>
<td>70</td>
<td>4000-6000 U</td>
<td>12500-17500 U</td>
<td>50-90 sec</td>
</tr>
<tr>
<td>Becker ‡</td>
<td>vte, ami, ua</td>
<td>61</td>
<td>70 U/Kg</td>
<td>15 U/Kg/h</td>
<td>51-80 sec</td>
</tr>
</tbody>
</table>

nr: not reported; na: not applicable.


† Dade: Dade actin thromboplastin (Baxter Health-care Corporation, Dade Division; Miami, FL); Dade FS: Dade actin FS (American Dade, Aguada, Puerto Rico); OA-aPTT: automated aPTT reagent (Organon Teknika Corp.; Durham, NC).

‡ In the nomogram group, patients with pulmonary embolism received a higher bolus dose (100 U/Kg).

§ Heparin infusion rate (U/h) = \( C_s \times k \times V \), where \( C_s \) = steady state plasma concentration of heparin (0.3 U/mL), \( k \) = elimination rate constant for heparin (0.832 h⁻¹), \( V \) = distribution volume of heparin (equal to the blood volume in mL).

¶ aPTT ratio

** In the nomogram group patients with pulmonary embolism received higher initial dosages (i.e. 100 U/Kg bolus, and 25 U/Kg/h initial dosage)

### Discussion

The current survey of clinical studies on the initial treatment of thromboembolic disorders with UFH clearly supports the advantage of nomogram-guided versus empirical administration of heparin in terms of both biological and clinical success rates. Patients in whom heparin was administered according to standardised guidelines did indeed achieve an adequate anticoagulation more promptly than patients treated empirically, and experienced a significantly lower rate.
Patients in the nomogram group were administered 3 different bolus dosages, according to weight-groups (less than 50, between 50 and 90, and more than 90 kg), that is 3500, 5000, and 7500 U. The continuous intravenous infusion was also based on body weight, being 2.1 ml/h or 1260 U/h (heparin solution concentration = 60 U per 0.1 ml) for an 80 kg person. For each 5 Kg increase/decrease in weight, the dose was adjusted ± 0.1 ml/h.

Enrolled patients were assigned one of 3 different initial UFH sc regimens, according to predefined weigh-groups (less than 50, between 50 and 70, and more than 70 kg). Initial UFH dosages were 4000 U intravenous bolus plus 0.5 ml subcutaneously for the first weigh group; 5000 U intravenously, plus 0.6 ml subcutaneously for the 2nd group; and a 6000 U bolus plus 0.7 ml subcutaneously for patients weighing more than 70 kg.

Cohort study, without control group.

<table>
<thead>
<tr>
<th>Reagent †</th>
<th>n.</th>
<th>Bolus (U)</th>
<th>Initial dosage (U/h)</th>
<th>aPTT Target</th>
</tr>
</thead>
<tbody>
<tr>
<td>nr</td>
<td>62</td>
<td>nr</td>
<td>nr</td>
<td>Nr</td>
</tr>
<tr>
<td>Dade</td>
<td>53</td>
<td>5000</td>
<td>1000</td>
<td>46-70 sec</td>
</tr>
<tr>
<td>Dade</td>
<td>42</td>
<td>5000</td>
<td>1041</td>
<td>1.5-2.0 §</td>
</tr>
<tr>
<td>Dade FS</td>
<td>57</td>
<td>5636</td>
<td>973</td>
<td>1.5-2.5 §</td>
</tr>
<tr>
<td>OA-aPTT</td>
<td>88</td>
<td>nr</td>
<td>1005±181</td>
<td>55-95 sec</td>
</tr>
<tr>
<td>nr</td>
<td>30</td>
<td>5570±389</td>
<td>1087±233</td>
<td>60-85 sec</td>
</tr>
<tr>
<td>nr</td>
<td>127</td>
<td>5000</td>
<td>24070±3576</td>
<td>60-85 sec</td>
</tr>
<tr>
<td>Dade FS</td>
<td>na</td>
<td>na</td>
<td>na</td>
<td>na</td>
</tr>
<tr>
<td>Dade FS</td>
<td>52</td>
<td>5000</td>
<td>1000</td>
<td>51-80 sec</td>
</tr>
</tbody>
</table>

†† Computer-assisted nomogram.

‡‡‡ Patients in the nomogram group were administered 3 different bolus dosages, according to weight-groups (less than 50, between 50 and 90, and more than 90 kg), that is 3500, 5000, and 7500 U. The continuous intravenous infusion was also based on body weight, being 2.1 ml/h or 1260 U/h (heparin solution concentration = 60 U per 0.1 ml) for an 80 kg person. For each 5 Kg increase/decrease in weight, the dose was adjusted ± 0.1 ml/h.

§§ Enrolled patients were assigned one of 3 different initial UFH sc regimens, according to predefined weigh-groups (less than 50, between 50 and 70, and more than 70 kg). Initial UFH dosages were 4000 U intravenous bolus plus 0.5 ml subcutaneously for the first weigh group; 5000 U intravenously, plus 0.6 ml subcutaneously for the 2nd group; and a 6000 U bolus plus 0.7 ml subcutaneously for patients weighing more than 70 kg.

§§§ Cohort study, without control group.

The observed reduction of VTE recurrent events in patients treated according to heparin nomograms supports the view that the rapid achievement of an adequate anticoagulation is a requisite of its efficacy. As patients treated according to guidelines received on average a definitely higher dose of heparin, the larger amount of injected drug is likely to be a major determinant of the observed advantage over empirical use. It is important to note that this advantage was not paid at the price of a higher number of bleeding events. Our quantitative analysis did not yield any significant difference.
Table 3 - Performance of the nomograms

<table>
<thead>
<tr>
<th>Leading author</th>
<th>Success rate*</th>
<th>Recurrent VTE</th>
<th>Bleedings</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pts†</td>
<td>Ctrs</td>
<td>Pts</td>
</tr>
<tr>
<td>Cruickshank‡</td>
<td>33/50</td>
<td>20/53</td>
<td>nr</td>
</tr>
<tr>
<td>Raschke‡†</td>
<td>60/62</td>
<td>37/48</td>
<td>2/41</td>
</tr>
<tr>
<td>Rivey‡</td>
<td>32/42</td>
<td>19/42</td>
<td>nr</td>
</tr>
<tr>
<td>Kershaw†‡</td>
<td>118/131</td>
<td>35/57</td>
<td>nr</td>
</tr>
<tr>
<td>Elliott‡</td>
<td>19/20</td>
<td>38/48</td>
<td>0/20</td>
</tr>
<tr>
<td>Gunnarsson§</td>
<td>35/45</td>
<td>48/88</td>
<td>nr</td>
</tr>
<tr>
<td>Hollingsworth§</td>
<td>52/81</td>
<td>30/82</td>
<td>nr</td>
</tr>
<tr>
<td>Brown‡</td>
<td>na</td>
<td>na</td>
<td>0/28</td>
</tr>
<tr>
<td>de Groot‡†</td>
<td>na</td>
<td>na</td>
<td>4/127§</td>
</tr>
</tbody>
</table>

Common 3.60 0.34 0.59 0.82

Odds Ratio¶** (2.64 to 4.92) †† (0.14 to 0.79) ‡‡ (0.20 to 1.72) §§ (0.39 to 1.74) ¶¶

nr: not reported, na: not applicable.

* Indicates the proportion of patients who reached the therapeutic threshold within 24 hours of treatment.
† Pts: patients in the nomogram groups; Ctrs: patients in the other heparin adjustment.
‡ Since the definition of the target aPTT was different between patients and controls, a formal comparison of success rate between groups was not considered justified by the authors themselves.
§ Indicate only case fatalities from pulmonary embolism, either diagnosed autopsically, either clinically by the attending physicians.
¶ 95% Confidence Intervals are reported in brackets.
** Statistical testing for sample heterogeneity was always non significant.
†† p=0.0001
‡‡ p=0.0013
§§ p=0.324
¶¶ p=0.615

between nomogram and control patients in the frequency of both major and minor bleedings, that in all studies was fully consistent with figures available from the literature. 27,10

Of course, the acceptance of the nomogram ‘philosophy’ is based on the validity of aPTT as standard test for UFH dose monitoring. This view has recently been challenged by several perspectives. First, there is no consensus on whether a higher risk of VTE recurrence is associated with subtherapeutic aPTT levels during the first 24 to 48 hours of treatment. A recent meta-analysis by Anand
et al. failed to demonstrate a relationship between subtherapeutic aPTT levels during the first 24 hours and the rate of VTE recurrence, provided patients had received at least 30,000 U of UFH per day. In contrast, two studies by Hull et al., based on the results of three double-blind randomized trials, reaffirmed the importance of rapidly achieving a therapeutic anticoagulation in order to prevent recurrent VTE. Ultimately, Anand et al. re-evaluated the results coming from three large multicenter trials comparing low-molecular weight heparins to UFH in the initial treatment of VTE. A subtherapeutic aPTT during the first 24 to 48 hours of treatment was not associated with a large increase in the risk of recurrent VTE. Notably, in all of the three original trials the investigators were strongly recommended to adjust UFH according to a nomogram. We can, therefore, hypothesise that the use of standard heparin according to an accepted nomogram for the treatment of acute VTE is likely to result in a favourable clinical outcome even in patients who fail to achieve a therapeutic aPTT in a timely fashion.

Second, Backer et al. challenged the accepted correlation between aPTT and heparin plasmatid levels. The authors, testing in a prospective study the agreement rate between aPTT values and anti-Xa activity, found a good correlation (more than 80% of cases) when the aPTT was within the therapeutic range, whereas the two tests disagreed in 61% of cases when the aPTT was overtherapeutic, and in 68.5% when the aPTT was subtherapeutic. In other words, some 70% of the patients were well anticoagulated although their aPTT was subtherapeutic. This observation is consistent with the results of a recent clinical study in patients requiring unusually large amounts of heparin. However, the feasibility of a routinary use of anti-Xa test instead of APTT for the monitoring of heparin therapy should be tested in a properly designed clinical trial on a larger set of patients.

Third, Brill-Edwards et al. challenged the reliability of the aPTT therapeutic range as an acceptable biological ‘marker’ of correct anticoagulation. They demonstrated that aPTT reagents provided by different manufacturers, and even reagent lots from the same manufacturer, yield considerable aPTT variation in response to equal amounts of heparin. To compensate for such variable response of aPTT reagents, it seems practical that the therapeutic range is established locally by using protamine titration heparin levels of 0.2 to 0.4 U/mL as the reference standard. Our survey supports the view that nomograms represents an effective, safe and cost-saving strategy for therapeutic UFH administration both in research settings and in community hospitals, and may conveniently be applied by
When administering UFH to patients with VTE, either intravenously or subcutaneously, a reasonable choice should always be a nomogram-based heparin adjustment, preferably according to body-weight.

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27. Hirsh J, Gent M. Recurrent venous thrombosis and heparin therapy: an evaluation of the


