

# ORIGINAL RESEARCH ARTICLE

## Achieving Target Antifactor Xa Activity with a Heparin Protocol Based on Sex, Age, Height, and Weight

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**Study Objectives.** To develop and validate an improved unfractionated heparin (UFH) dosage protocol, using antifactor Xa levels as the outcome variable.

**Design.** Prospective case series.

**Setting.** A 625-bed, adults-only, private, tertiary care teaching hospital.

**Patients.** Three hundred seventy-two patients receiving UFH for eight different indications were in the protocol derivation group. One hundred ninety-seven patients were in the final validation group.

**Intervention.** Variables that predicted successful UFH treatment were determined by analysis of variance and regression.

**Measurements and Main Results.** Sex, age, height, weight, UFH dosage, and antifactor Xa levels were variables. A regression model using sex, age, height, and weight was superior to a weight-only model in predicting UFH dosage. Target-range antifactor Xa levels were achieved with the new protocol in 122 (87%) of 140 patients within 24 hours of start of therapy.

**Conclusion.** A UFH dosage protocol based on patient sex, age, height, and weight produced improved initial target antifactor Xa levels compared with a weight-based protocol. The protocol is computerized and easy to apply.

**Key Words:** unfractionated heparin, dosage protocol, antifactor Xa activity. (Pharmacotherapy 2004;24(6):713–719)

The reference standard for monitoring heparin therapy is plasma antifactor Xa or antifactor IIa activity.<sup>1–3</sup> Antifactor Xa activity is used more frequently because it can measure both unfractionated heparin (UFH) and low-molecular-weight heparin (LMWH). The activated partial thromboplastin time (aPTT) has been widely used as a surrogate monitoring test for UFH therapy, but it must be calibrated to an antifactor Xa or antifactor IIa assay before use.<sup>3</sup> However, correlation of aPTT with the antifactor

Xa assay is only modest.<sup>4–6</sup> In addition, the aPTT is falsely elevated by concomitant warfarin therapy,<sup>7</sup> is falsely lowered by elevated factor VIII levels,<sup>8</sup> and can be extremely variable among laboratories.<sup>5, 9, 10</sup>

Although large human clinical outcome studies comparing aPTT with antifactor Xa or antifactor IIa have not been performed, there are reports showing better correlation of clinical outcomes with antifactor Xa assays than with aPTT.<sup>11–14</sup> An important rabbit thrombosis study showed that antifactor IIa levels were a more reliable predictor of antithrombotic effectiveness than were aPTT values.<sup>15</sup>

The target antifactor Xa activity for UFH therapy is 0.3–0.7 U/ml as measured by a chromogenic amidolytic assay.<sup>1–3</sup> It is logical, although not proved, that optimal UFH therapy would occur if dosage protocols quickly achieved and maintained this target antifactor Xa range.

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Most UFH protocols use a patient's actual<sup>3, 16-21</sup> or ideal<sup>22-26</sup> body weight to determine loading and maintenance infusion dosages. However, UFH is distributed in the blood volume,<sup>27-32</sup> and, accordingly, dosage based on a patient's weight may be less accurate in patients who are obese or very lean since fat is less vascular than lean body mass.<sup>20, 33-35</sup>

We previously reported that the combination of sex, age, height, and weight better predicted a patient's initial antifactor Xa activity response to UFH than weight alone.<sup>36</sup> In this study, we developed, implemented, and sought to validate a UFH protocol based on these four patient variables.

## Methods

### Patients

Since 1998, only antifactor Xa has been used to monitor heparin therapy at our institution. In 1999, we instituted a hospitalwide, nurse-managed paper protocol that used patient sex, age, height, and weight to determine initial UFH dosage and used antifactor Xa levels to subsequently adjust the maintenance dosage. This initial protocol was derived from pharmacologic data obtained from a previously reported series of 268 patients.<sup>36, 37</sup> The protocol targeted an antifactor Xa range of 0.3–0.7 U/ml and obtained the first level 8 hours after the start of therapy to ensure that the level was at, or near, steady state.<sup>38, 39</sup> The UFH loading dose was 450 U/L of estimated blood volume, which was predicted to give an immediate plasma antifactor Xa level of approximately 0.5 U/ml, assuming an average hematocrit level and some degree of heparin binding in the distribution space. This loading dose is less than that used by many protocols,<sup>3, 19-21</sup> but our initial patient series<sup>36</sup> and the work of others<sup>32, 38-40</sup> showed that typical loading doses of 70–80 U/kg often produce supratherapeutic initial antifactor Xa levels.

After a brief trial period, we prospectively followed all patients who were administered UFH during the remainder of 1999, during which time this protocol was the only therapeutic intravenous UFH protocol used at our institution. The 372 consecutive patients included in this report met the following criteria: they had at least 16 continuous hours of UFH treatment, had the first antifactor Xa level measured 7–9 hours after the start of therapy, and had at least two antifactor Xa monitoring tests performed. Concomitant warfarin therapy was not excluded and was used in about half of these patients.

The study was reviewed by the institutional review board and met the criteria for exempt review.

### Patient Data

Data collected or calculated were sex, age, height (sometimes patient stated rather than measured), actual weight, body mass index (actual kg/m<sup>2</sup>), and estimated blood volume<sup>41</sup> (Appendix 1). The timing and dosage of UFH along with the timing and results of antifactor Xa monitoring were recorded for each patient. The UFH dosage for each patient was expressed as cumulative U/hour, calculated by dividing the total amount of UFH received by the number of treatment hours. Average antifactor Xa levels over the entire treatment course were calculated for each patient by using an area under the curve method described previously.<sup>42</sup> Our particular focus was patients with average antifactor Xa levels of 0.3–0.55 U/ml, since there is better agreement that this lower end of the 0.3–0.7 U/ml antifactor Xa range is therapeutic and safe for most patients.<sup>43</sup>

### Antifactor Xa Assay

Blood samples were collected directly into 0.105-mol/L (3.2%) sodium citrate coagulation tubes (BD Vacutainer; Becton Dickinson Co., Franklin Lakes, NJ), and the samples were centrifuged for 10 minutes at 3000 x g. Plasma was sampled in the coagulation analyzer directly from the centrifuged tubes to minimize platelet activation. All samples were assayed within 2 hours of collection for antifactor Xa with the STA Hemostasis System (manufactured by Diagnostica Stago, Asnières-sur-Seine, France, and distributed in the United States by American Bioproducts Company, Parsippany, NJ). The antifactor Xa assay used was Rotachrom Heparin (American Bioproducts), an amidolytic, one-step competitive inhibition antifactor Xa assay in which chromogenic substrate CBS 52.44 is used without the addition of exogenous antithrombin. Samples with greater than 1.1 U/ml were not further diluted and were reported as 1.1 U/ml for this study.

### Statistical Analyses

Descriptive statistics, group comparisons, analysis of variance, and regression analysis were performed with Statview 4.5 and JMP (SAS Institute, Inc., Cary, NC). Descriptive statistics for all variables are reported as medians and

**Table 1. Demographics and Results in 372 Patients Treated with the Initial Unfractionated Heparin Protocol**

Variable	Median	Range	Sex Difference (p value) <sup>a</sup>
Age (yrs)	71	17–98	0.40
Actual weight (kg)	77	30–184	<0.0001
Height (in.)	66	57–80	<0.0001
Body mass index	27	14–65	0.52
Blood volume (L)	4.7	2.3–8.5	<0.0001
Length of therapy (hrs)	64	17–309	0.21
UFH (U/hr)	1170	541–2326	<0.0001
UFH (U/hr/kg of actual weight)	15.2	9–24.6	<0.0001
UFH (U/hr/L of blood volume)	0.25	0.16–0.37	0.76
Average antifactor Xa level (U/ml)	0.47	0.11–0.96	0.20

UFH = unfractionated heparin.

<sup>a</sup>Mann-Whitney *U* test for difference. The sample comprised 182 men and 190 women.

ranges because most variables had nonnormal distributions. Group comparisons of variables were performed by using nonparametric tests. A *p* value of 0.05 or less was considered to indicate a statistically significant difference.

## Results

Table 1 shows the demographic and treatment results for the 372 patients treated with the initial paper protocol. Men and women were represented equally in the series. As expected, men were taller, heavier, had greater estimated blood volume, and received more units of UFH/hour. Men also received more UFH/hour on a weight basis (16.0 U/kg/hr for men vs 14.3 U/kg/hr for women, *p*<0.0001). However, men and women received the same amount of UFH/L of estimated blood volume/hour and had equivalent average antifactor Xa levels (0.47 U/ml).

Table 2 shows the indications for UFH treatment in the 372 patients. Acute venous thromboembolism accounted for 28% of the indications; the remaining 72% comprised arterial and cardiac indications. Men and women did not differ in their indications for therapy.

Of the 372 patients, 245 (66%) had average antifactor Xa levels of 0.3–0.55 U/ml and were the subject of further analysis. This subgroup was otherwise equivalent to the entire patient group, including indication for therapy. The excluded 127 patients were assumed to have been unusually sensitive or resistant to UFH.

Analysis of variance was used to test patient factors for their ability to predict UFH dosage in the 245 patients. Sex, age, height, and weight were each found to predict UFH dosage independently (*p*<0.0001 for each variable). Body mass index was not an independent

**Table 2. Indications for Unfractionated Heparin Therapy in the 372 Patients**

Indication	No. (%) of Patients
Coronary artery disease	84 (23)
Atrial fibrillation	69 (19)
Deep vein thrombosis (acute)	63 (17)
Cerebral vascular disease	58 (16)
Pulmonary embolism (acute)	40 (11)
Artificial heart valve	27 (7)
Peripheral vascular disease	15 (4)
Systolic heart failure	16 (4)

Percentages are rounded to the nearest whole number.

predictor of UFH dosage. Estimated blood volume, which included height, weight, and sex in its calculation (Appendix), substituted completely for these three variables in the analysis of variance model. Larger blood volume and younger age were predictive of higher UFH dosage requirement.

A regression model using blood volume and age as independent variables had an *R*<sup>2</sup> value of 0.83 for predicting UFH dosage. In contrast, a regression model that used weight as the sole predictor of UFH dosage had an *R*<sup>2</sup> value of 0.65, indicating that weight alone was only 78% as accurate as blood volume and age for predicting UFH dosage. The blood volume and age regression equation (Appendix 1) was used in the next and all subsequent revisions of the UFH therapeutic protocol.

Dosage in the protocol was adjusted by proportionately increasing or decreasing the UFH infusion in response to antifactor Xa levels. The adjustment scheme was refined empirically 3 times during the next 3 years by using antifactor Xa results from three additional series of patients. Analysis of UFH loading and infusion doses was

**Table 3. Proportional Dosage Adjustment for the Unfractionated Heparin Protocol**

Antifactor Xa Level (U/ml)	Dosage Adjustment Factor
0–0.15	1.4
0.16–0.25	1.25
0.26–0.35	1.2
0.36–0.40	1.175
0.41–0.60	1.0
0.61–0.70	0.8
0.71–0.80	0.75
0.81–0.90	0.7
0.91–1.0	0.625
1.01–1.1	0.6
> 1.1	0.575

not performed on these additional patients. The proportional dosage adjustment method used in our current protocol is shown in Table 3.

We also worked with the nursing staff to improve the application of the protocol by computerizing and centrally deploying it as a Microsoft Excel (Microsoft Corp., Redmond, WA) workbook that uses incremental, menu-driven data entry. This approach reduces errors, increases the speed of calculation, and produces a hard-copy record of the data and dosage recommendations for the patient chart.

Table 4 shows the antifactor Xa results from our most recent validation series of 197 consecutive patients starting UFH treatment with the computerized protocol at the end of 2003. Only patients in whom the protocol was accurately and continuously applied were included. The first antifactor Xa level was obtained 7–9 hours after start of therapy, the second level 16–24 hours after therapy began, and the third level 24–36 hours after start of therapy. The first antifactor Xa level was in the target range (0.3–0.7 U/ml) for 62% of the patients, the second level for 87% of the patients, and the third level for 86%.

We consider antifactor Xa levels greater than 0.8 U/ml and those less than 0.2 U/ml to be of potentially more serious consequence for patients than levels just above or below the target range. Using these cutoffs, Table 4 shows the protocol was successful for 79% of patients at 8 hours, 94% of patients at 16–24 hours, and 93% of patients at 24–36 hours. There were fewer patients who had second and third levels measured because UFH therapy was needed for only a short period and was discontinued in some patients before a second level was obtained (e.g., patients with unstable coronary syndrome who underwent coronary angiography).

### Discussion

To our knowledge, this is the largest study to investigate UFH dosage by using antifactor Xa as the pharmacologic outcome variable. Target range antifactor Xa levels (0.3–0.7 U/ml) were achieved in 62% of 197 patients at 8 hours. In the only directly comparable study, we reported on a series of 92 patients treated with an ideal-weight-based protocol, which was typical of most weight-based protocols and included administration of a higher loading dose.<sup>36</sup> Only 37% of patients in that series had initial 6-hour antifactor Xa levels in the target range.

Other large studies of UFH dosage have used the aPTT as the pharmacologic outcome variable. Since antifactor Xa levels were not measured in these studies, caution must be used when comparing our findings with the results of these studies. In a frequently cited weight-based protocol, which used an antifactor Xa-calibrated aPTT, 57% of 62 aPTT levels were within the therapeutic range at 24 hours.<sup>19</sup> In a more recent large study of patients with unstable coronary syndrome, therapeutic aPTT levels using uncalibrated assays were achieved in 52% of approximately 5000 patients at 24 hours.<sup>44</sup> In

**Table 4. Antifactor Xa Level Findings in 197 Patients Treated with the Blood Volume- and Age-Based Unfractionated Heparin Protocol**

Antifactor Xa Level (U/ml)	7–9 Hours (n=197)	16–24 Hours (n=140)	24–36 Hours (n=101)
Median	0.61	0.52	0.46
	No. (%) of Patients		
> 0.8	31 (16)	7 (5)	5 (5)
0.71–0.80	19 (10)	3 (2)	0 (0)
0.3–0.7	123 (62)	122 (87)	87 (86)
0.2–0.29	13 (7)	6 (4)	7 (7)
< 0.2	11 (6)	2 (1)	2 (2)

comparison, 87% of 140 patients in our series achieved target range antifactor Xa levels at 24 hours.

Previous pharmacologic studies suggested that blood volume would be a stronger predictor of UFH dosage than weight alone since heparin is distributed in the blood volume.<sup>27-32</sup> It is likely that the sex difference in UFH requirement noted in this study and others<sup>45, 46</sup> is predominantly related to the differences in lean mass and blood volume between men and women of the same height and weight.<sup>47</sup> Older patients required less UFH in this series; although the reason for this is unknown, this result has been described by others.<sup>3, 21, 46, 48, 49</sup> Although serum creatinine values were not available for all of our patients, we did not see an independent association of estimated creatinine clearance with UFH requirements in this study or in our previous studies. Thus, the age effect seems to be independent of renal function.

The initial UFH dosage prescribed by this protocol does not produce optimal results for all patients. Part of the inaccuracy results from the estimation of patient blood volume since two individuals of the same sex, height, and weight may have different blood volumes due to differences in adiposity, disease state, nutritional state, or other confounding variables.<sup>47</sup> Disease states, and perhaps inherited conditions, can also alter proteins in the blood that affect UFH dosage requirements.<sup>3, 50-53</sup>

In a previous report, we showed that heparin resistance, as detected with antifactor Xa, is not different between arterial and venous thrombotic conditions.<sup>54</sup> Rather, we found that a lower hemoglobin concentration is a marker of an increased likelihood of heparin resistance. Thus, it is likely that our protocol will perform less well in patients with extremes of hemoglobin concentration. Finally, smoking, a variable not considered in this study, may have an effect on heparin distribution and kinetics.<sup>21, 45, 55, 56</sup> For all of these reasons, monitoring and adjustment of UFH dosage is still required for all patients.

Frequently, LMWH is dosed based on actual body weight and without monitoring. However, various patient variables also affect LMWH pharmacokinetics, and similarly improved results in some patients may be obtained with the use of more sophisticated initial dosage protocols and antifactor Xa monitoring.<sup>57-63</sup>

Although there are a number of reasons why the antifactor Xa assay is superior to the aPTT for heparin monitoring, we do not know that our protocol achieves superior clinical results, only that it achieves superior target range antifactor Xa results. We previously showed that the net incremental cost/patient of using antifactor Xa monitoring instead of aPTT monitoring was very small and an unconvincing reason to avoid adopting antifactor Xa monitoring for heparin therapy.<sup>37</sup>

## Conclusion

We have shown that initial target range antifactor Xa levels can be achieved more accurately when initial UFH dosage is based on a patient's sex, age, height, and weight compared with weight alone. A computerized protocol incorporating this initial dosage calculation, as well as proportionate dosage adjustment in response to antifactor Xa levels, is straightforward for the nursing staff to use and reduces errors. The LMWH and other newer antithrombotic agents should not be declared superior to UFH until they are compared with a more accurate UFH protocol, such as the one described in this report.

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A copy of the Microsoft Excel workbook protocol is available by e-mail from the authors. Also available is a Visual Basic version of the protocol configured for use in Pocket PC handheld computer devices.

## Appendix 1. Equations Used in the Heparin Dosage Protocol

Estimated blood volume (L)<sup>41</sup>:

Men:  $(0.3669 \cdot \text{height in m}^3) + (0.03219 \cdot \text{weight in kg}) + 0.6041$

Women:  $(0.3561 \cdot \text{height in m}^3) + (0.03308 \cdot \text{weight in kg}) + 0.1833$

Unfractionated heparin dosage:

Loading dose (U) =  $450 \cdot \text{estimated blood volume (L)}$

Initial infusion rate (U/hr) =  $344.335 + (\text{estimated blood volume in L} \cdot 257.962) - (\text{age in yrs} \cdot 4.951)$

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