Unfractionated Heparin Dosing Nomograms: Road Maps to Where?

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Weight-adjusted nomograms have been a significant advance in the use of unfractionated heparin (UFH). Clinical trials have demonstrated the ability of weight-adjusted nomograms to achieve a therapeutic activated partial thromboplastin time (aPTT) more rapidly than with standard UFH dosing. Despite this advantage, a significant number of patients have subtherapeutic and supratherapeutic aPTTs. Real-world experiences also corroborate the inability to keep UFH therapeutic with the use of nomograms. Despite the limitations of UFH nomograms, they have been used in several different types of venous and arterial thrombosis treatment settings. Unfortunately, these nomograms are not all consistent and require a considerable amount of time for training health care professionals on their use in order to limit the potential for medication errors. Although UFH nomograms have provided advancement over standard UFH dosing, their limitations still generate the desire for a more predictable anticoagulant.

Key Words: nomograms, unfractionated heparin, activated partial thromboplastin time, thrombosis, weight-based dosing, standard dosing.

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For many years, patients received a standard dosage of unfractionated heparin (UFH), consisting of a 5000-U bolus followed by a 1000-U/hour infusion, for treatment of venous and arterial thrombosis. Later, studies found that UFH dosage adjustments based on the patient's weight provided therapeutic anticoagulation more rapidly.[1–3] In the treatment of venous thromboembolism (VTE), a more rapid therapeutic anticoagulation method demonstrated a reduction in recurrent VTE events without increasing major bleeding.[4, 5] Use of a weight-adjusted UFH nomogram quickly became a standard of practice for acute treatment of VTE.

Utility in Question

Use of weight-adjusted UFH was investigated in the treatment of arterial thrombosis. Studies determined that less UFH was needed to treat arterial disease than venous disease. Weight-adjusted UFH was associated with less bleeding than standard UFH dosing, and maintained clinical efficacy.[6, 7] As consensus guidelines began to recommend weight-adjusted UFH for management of arterial thrombosis, many institutions integrated these recommendations into treatment protocols and nomograms.

Weight-adjusted nomograms have provided an advantage over standard UFH dosing. In one study, a greater percentage of patients achieved an initial activated partial thromboplastin time (aPTT) greater than 1.5 times the control with weight-based UFH dosing (86%) compared with standard dosing (32%).[4] In addition, the rate of VTE recurrence was 5 times higher with standard UFH dosing (Table 1).

In another study, 66% of patients prescribed UFH nomogram-based dosing achieved a therapeutic aPTT within 24 hours.[8] By contrast, only 37% of a retrospective control sample of patients prescribed UFH based on empirically determined dosage achieved a therapeutic aPTT

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Table 1. Outcomes with Weight-Based versus Standard Heparin Dosing Nomograms

Outcome	Weight-Based Dosing	Standard Dosing	p Value
aPTT (% of patients)			
First value > 1.5 times control	86	32	<0.001
Value > 1.5 times the control within 24 hrs	97	77	<0.002
Value in therapeutic range within 24 hrs	89	75	0.08
No. of dosage adjustments/patient	2.67	3.96	<0.001
Adverse events, no. (%) of patients			
Major bleeding	0	1/52 (2)	0.45
Minor bleeding	2/63 (3)	2/52 (4)	1.00
Recurrent VTE	2/41 (5)	8/32 (25)	0.02

aPTT = activated partial thromboplastin time; VTE = venous thromboembolism.
Adapted from reference 4.

Table 2. Percentages of aPTT Values Within Clinically Relevant Ranges

Time	Weight-Based Dosing	Standard Dosing
Within first 24 hrs		
Within therapeutic range	57	35
Subtherapeutic	15	58
Supratherapeutic	27	7
Within first 48 hrs		
Within therapeutic range	65	44
Subtherapeutic	18	49
Supratherapeutic	18	8

aPTT = activated partial thromboplastin time.
p<0.001 for all comparisons, weight-based vs standard dosing.
Adapted from reference 4.

Table 3. Risk of Recurrence of Thromboembolic Events if Lower Limit of Therapeutic aPTT Range Was Not Achieved Within 24–48 Hours

Year Reported	Condition	Outcome	Relative Risk
1986	DVT	Recurrent DVT	15.0
1972	DVT	Recurrent DVT	10.7
1989	Acute MI	LV thrombus	22.2
1987	Acute MI	Recurrent MI or angina	8.0
1988	Acute MI	Recurrent MI or angina	13.3
1993	DVT	Recurrent DVT	4.5

aPTT = activated partial thromboplastin time; DVT = deep vein thrombosis; MI = myocardial infarction; LV = left ventricle.
Adapted from reference 10, modified from reference 4.

within 24 hours. Finally, another study found that the time to reach a therapeutic aPTT with UFH standard dosing (20.7 ± 11.9 hrs) was significantly longer than was required with nomogram-based dosing (13.1 ± 11.9 hrs; p=0.02).[5] In addition, a greater percentage of patients receiving nomogram-based dosing achieved a therapeutic aPTT at 12 (p=0.002) and 24 hours (p=0.009).

Even with UFH weight-based dosing, it is difficult to achieve a therapeutic aPTT consistently. Clinical trials have reported that rates of nontherapeutic aPTTs approach 50% during the first 24–48 hours of weight-based UFH therapy.[4, 5, 9] Specifically, one study reported that 42% and 36% of aPTTs measured within the first 24 and 48 hours, respectively, were not within the therapeutic range.[4] Even more concerning, approximately 20% of the aPTT results were subtherapeutic within the first 48 hours (Table 2).

In terms of clinical and economic outcomes, more thrombotic complications and higher costs are associated with treatment in patients with subtherapeutic aPTTs.[4, 5, 9, 10] These clinical outcomes were summarized in a retrospective subgroup analysis of cohort studies.[10] This analysis demonstrated an increase in recurrent thromboembolic events in patients with subtherapeutic aPTTs compared with event rates in patients with therapeutic aPTTs (Table 3).[4, 10]

In reviewing a real-world practice setting, a retrospective study assessed weight-based UFH therapy and identified additional limitations of this regimen.[11] When the initial aPTT value was therapeutic in the patient population studied, it was maintained at the next measurement in only 29% of patients. Also, during the first 3 days of UFH therapy, 61% of patients had at least four different infusion doses, and 42% needed additional bolus dosing.

In summary, these trials and practice reviews recognized that weight-based UFH dosing was an improvement over standard UFH dosing. However, this method clearly does not represent optimal anticoagulation.

One difficulty with the use of weight-adjusted UFH nomograms is the wide variation of aPTT

therapeutic ranges for UFH among institutions. If one institution appropriately establishes and validates its therapeutic range and that range is different from the one used in key clinical trials, all adjustments based on the trial range could be flawed.

For example, due to the positive outcomes with one study's weight-based UFH nomogram,[4] it was widely adopted as the standard of practice throughout medical institutions. Unfortunately, this often occurred without realization that the guiding aPTT values published in that study—and therefore the nomogram—were valid only at the site where the nomogram was developed. This meant that other sites adopting the nomogram would need to determine their own target aPTT range, adjust the nomogram accordingly, and follow up with a routine assessment of clinical outcomes. Thus, if an institution failed to establish its own validated therapeutic range, using published dosage and aPTT targets could lead to subtherapeutic or supratherapeutic anticoagulation. This problem is also evident in the treatment of arterial disease. Although the initial bolus dose and infusion rate are weight based, there are no recommendations for weight-based adjustments.[6, 7]

Another issue is the number of nomograms that may exist at any one institution. The UFH dosage for patients with VTE most often is determined according to the nomogram in the study cited above (80-U/kg bolus, 18-U/kg/hr infusion; Table 4).[4] Several other nomograms, however, have been used in treatment of arterial thrombosis. According to one nomogram, the UFH dosage for patients receiving fibrinolytic therapy for treatment of ST-segment elevation myocardial infarction is a 60-U/kg bolus (maximum 4000 U) followed by a 12-U/kg/hour infusion (maximum 1000 U/hr).[6] The UFH dosage for the same patients not receiving fibrinolytic therapy would be determined using a different UFH nomogram, which calls for a 70-U/kg bolus (maximum 5000 U) followed by a 15-U/kg/hour infusion (maximum 1000 U/hr).[6] The dosage for patients with acute coronary syndromes but without ST-segment elevation again may be determined using a different UFH nomogram.[7]

The choice of nomogram usually differs based on the decision to use a glycoprotein IIb-IIIa inhibitor and may differ depending on which glycoprotein IIb-IIIa inhibitor is selected. The UFH nomogram also could be different depending on the decision to send the patient for percutaneous coronary intervention or to treat medically. Other UFH nomograms also may exist for use in patients with stroke or bridging during surgical procedures.

Table 4. Weight-Based Dosing Nomogram for UFH

Indicator for Dosage Change	Bolus Dose	Infusion Rate
Baseline, start of therapy	80 U/kg	18 U/kg/hr
aPTT (sec)[a]		
< 35	80 U/kg	Increase by 4 U/kg/hr
35–45	40 U/kg	Increase by 2 U/kg/hr
46–70	No change	No change
71–90	None	Reduce by 2 U/kg/hr
> 90	None	Hold for 1 hr and reduce by 3 U/kg/hr

UFH = unfractionated heparin; aPTT = activated partial thromboplastin time.
[a]Target aPTT of 46–70 sec was determined with reagent and equipment used to correlate with a heparin level of 0.38–0.57 IU/ml of antifactor Xa activity. The aPTT determination was repeated 6 hrs after any dosage change.
Adapted from reference 4.

The numerous UFH nomograms that can exist within one institution can be problematic. Physicians, pharmacists, and nurses all need extensive training in using each nomogram and in knowing the differences among the different nomograms. Teaching institutions must require continuing training for new staff on the use of the nomograms to ensure appropriate patient care. Despite exhaustive training in the use of UFH, the large number of available nomograms provides enormous potential for medication errors and negative patient outcomes.

Conclusion

Despite the potential advantage of achieving rapid therapeutic anticoagulation with UFH, weight-adjusted UFH nomograms have major drawbacks. Many patients still do not achieve a timely therapeutic aPTT, different nomograms are used for different patient groups, continuing training is extensive and costly, and the potential for medication errors is enormous. In addition, weight-based nomograms validated through clinical trials are not directly applicable to other institutions. Therefore, each institution must determine its own target therapeutic aPTT range and follow up with routine assessments of clinical outcomes. For these reasons, an anticoagulant that produces a more predictable response and does not require the use of dosing nomograms is desirable. Recommendations of the Heparin Consensus Group for using UFH dosing nomograms are provided in Appendix 1.

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Appendix 1. Recommendations for Using Unfractionated Heparin Dosing Nomograms

1. The number of institutional UFH dosing nomograms should be consolidated and validated in practice to avoid confusion and minimize errors.
2. Establishing a continuing education plan regarding the UFH nomograms for all appropriate members of the health care team is advised.
3. The therapeutic range for aPTT contained in UFH nomograms should be determined by each laboratory and should be revalidated for each change in reagent, reagent lot, and reagent-instrument combination.
4. Clinical outcomes of UFH dosing nomograms should be regularly assessed.