

Suboptimal Monitoring and Dosing of Unfractionated Heparin in Comparative Studies with Low-Molecular-Weight Heparin

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Background: Site-specific validation of the activated partial thromboplastin time (aPTT) therapeutic range is required to ensure administration of the optimal dose of unfractionated heparin. Therapeutic ranges of 1.5 to 2.5 times the control value are subtherapeutic for most modern aPTT reagents.

Purpose: To audit the appropriateness of aPTT monitoring in clinical trials comparing unfractionated heparin and low-molecular-weight heparin in patients with venous thromboembolism.

Data Sources: Search of PubMed database from 1984 to 2001.

Study Selection: Randomized, controlled trials that compared unfractionated and low-molecular-weight heparin for the treatment of venous thromboembolism.

Data Extraction: Use of unvalidated and potentially suboptimal

therapeutic ranges for aPTT in patients assigned to receive unfractionated heparin.

Data Synthesis: Fifteen studies met inclusion criteria. Only 3 studies used a validated aPTT therapeutic range, and 11 studies used a range that included aPTT values 1.5 times the control value. Ten studies reported unfractionated heparin doses, and 7 of these documented a reduction to less than 30 000 U/d in response to aPTT results.

Conclusions: Most studies monitored unfractionated heparin inappropriately. This shortcoming could be responsible for the reduced efficacy of unfractionated heparin in clinical trials.

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Many randomized, controlled trials (1–15) have compared the relative efficacy and safety of low-molecular-weight heparin (LMWH) and unfractionated heparin in treating venous thromboembolism. Several meta-analyses of these trials have reported that LMWH provides superior clinical outcomes (16, 17). These results could be influenced by bias if clinical trials administered unfractionated heparin in a suboptimal manner.

When unfractionated heparin is used to treat venous thromboembolism, efficacy and safety depend on the use of an optimal activated partial thromboplastin time (aPTT) therapeutic range to adjust the heparin dose. In the 1970s, an aPTT ranging from 1.5 to 2.5 times the control value was associated with a reduced risk for recurrent thromboembolism and correlated with heparin levels of 0.2 to 0.4 IU/mL by protamine titration. A heparin level of 0.2 to 0.4 IU/mL by protamine titration was subsequently equivalent to an anti-factor Xa heparin level of 0.3 to 0.7 IU/mL. This aPTT range (1.5 to 2.5 times control) and associated heparin levels were considered to be the optimal therapeutic range for treating venous thrombosis and gained wide clinical acceptance.

However, the reagents and instruments used to determine the aPTT have changed substantially in the past 25 years. More than 300 different laboratory methods are in use, and wide variation in their responsiveness to the anticoagulant effect of heparin has become apparent. This variability is largely due to differences among thromboplastin reagents, but differences in specific lots of reagent and coagulometer instrumentation are also important (18, 19). The magnitude of this variability is such that aliquots of plasma containing a heparin concentration equivalent to 0.3 IU/mL (by factor Xa inhibition) yield mean aPTT results ranging from 48 to 108 seconds, depending on the laboratory method used (18–19). Thus, a target aPTT

range of 60 to 85 seconds could be subtherapeutic, therapeutic, or supratherapeutic, depending on the aPTT reagent laboratory method used for clot detection.

Modern thromboplastin reagents are also more sensitive than the reagents used to establish the traditional aPTT therapeutic range of 1.5 to 2.5 times the control value. As a result, the aPTT ratios of a plasma sample containing therapeutic concentrations of heparin vary from 1.6 to 2.7 times the control value to 3.7 to 6.2 times the control value with modern thromboplastin reagents (Table 1) (18, 19). Therefore, the use of a fixed aPTT therapeutic range of 1.5 to 2.5 times the control value will result in unfractionated heparin underdosing in many institutions.

The College of American Pathologists (20), the American College of Chest Physicians (21), and others have recommended against the use of an aPTT therapeutic range based on an aPTT ratio, such as 1.5 to 2.5 times the control value. Instead, they recommend that the therapeutic aPTT range be calibrated specifically for each reagent lot or coagulometer by determining the aPTT values that correlate with therapeutic heparin levels—equivalent to 0.3 to 0.7 IU/mL by factor Xa inhibition. Clinical trials comparing LMWH with unfractionated heparin should use this method at each study site to ensure that unfractionated heparin adjustments result in optimal unfractionated heparin dosage (>30 000 U/d [21]).

We performed a literature search to identify randomized trials comparing LMWH with unfractionated heparin in venous thromboembolism. Our primary aim was to audit the appropriateness of aPTT monitoring. We hypothesized that suboptimal methods of unfractionated heparin monitoring and dose adjustment might be prevalent. If this was the case, it could contribute to the reported superiority of LMWH over unfractionated heparin in recent meta-analyses.

METHODS

Study Identification

We performed a literature search from 1984 to 2001, using the National Library of Medicine's PubMed database with the following search logic: *heparin* or *low molecular weight heparin* (Medical Subject Headings [MeSH] terms), *deep venous thrombosis* or *pulmonary embolism* (MeSH terms), and *randomized, controlled trial* (publication type). We searched the bibliographies of selected articles.

Study Eligibility

We selected only published articles that randomly assigned patients with venous thromboembolism to subcutaneous LMWH and intravenous unfractionated heparin, reported original data, and used objective measures to assess symptomatic recurrent thromboembolism and major bleeding.

Data Extraction

We extracted the following data on each of the selected studies: number of study sites; definition of aPTT therapeutic range; whether the studies validated aPTT therapeutic range; whether the studies specified a protocol for unfractionated heparin dose adjustment; whether the studies reported the percentage of patients with therapeutic aPTT at 24 to 48 hours; and the steady-state dose of unfractionated heparin—defined as the mean dose administered at the latest reported point in treatment after the first day. Rates for major bleeding and symptomatic, radiographically confirmed, recurrent thromboembolism with at least 30 days' follow-up were also collected.

RESULTS

We identified 15 studies that met inclusion criteria (1–15). Table 2 lists the rate of recurrent thromboembolism and major bleeding for each study. Only 3 studies stated that they used a validated aPTT therapeutic range; 10 studies used aPTT ranges that included values 1.5 times the control value (Table 2). Only 2 studies reported a standardized protocol by which the unfractionated heparin dose was adjusted (3, 9), and 4 studies reported the percentage of patients achieving therapeutic aPTTs (2, 8, 12, 13). Ten studies reported the steady-state unfractionated heparin dose, and 7 of these documented a reduction in

Context

Efficacy and safety of unfractionated heparin in thromboembolic disease depend on accurate measurement of the adjusted partial thromboplastin time (aPTT). Failure to standardize aPTT measurement may have led to wide variation in unfractionated heparin dosing in previous studies that showed superiority of low-molecular-weight heparin (LMWH) to unfractionated heparin.

Contribution

A survey of published randomized, controlled trials comparing LMWH with unfractionated heparin shows that few of the studies used validated aPTT therapeutic ranges or standardized protocols for adjusting unfractionated heparin dose.

Implications

While this study does not show that variations in aPTT measurement account for the apparent superiority of LMWH to unfractionated heparin, it highlights some serious methodologic concerns.

—The Editors

the unfractionated heparin infusion rate to less than 30 000 U/d in response to aPTT results.

DISCUSSION

Our results demonstrate a potential source of bias in clinical trials comparing LMWH with unfractionated heparin for treating patients with venous thromboembolism. Most trials used unvalidated aPTT therapeutic ranges that could lead to suboptimal dosing with unfractionated heparin. Most trials did not specify the manner in which unfractionated heparin dose was adjusted, did not report the percentage of patients achieving therapeutic aPTT values, and did not document that patients were treated with an optimal steady-state unfractionated heparin dose (>30 000 U/d [21]).

In our review, three studies reportedly used validated aPTT therapeutic ranges (1, 10, 11). Site-specific validation of the aPTT therapeutic range is important because it allows a uniform interpretation of aPTT results that is independent of variation in reagents used at different clinical

Table 1. Activated Partial Thromboplastin Time Therapeutic Ranges for Representative Modern Thromboplastin Reagents, Determined by Validated Method*

Reagent	Therapeutic aPTT, s	Therapeutic aPTT Ratio	Year	Reference
Actin (Dade Diagnostics, Aguada, Puerto Rico)	49–92 to 49–109	1.9–3.7 to 2.1–4.6	2001	18
Actin FS (Dade Diagnostics, Aguada, Puerto Rico)	60–85	1.8–2.5	1989	17
	79–105	2.3–3.0	1991	17
	72–119 to 98–165	2.6–4.3 to 3.7–6.2	2001	18
Actin FSL (Dade Diagnostics, Aguada, Puerto Rico)	57–98 to 84–124	2.1–3.5 to 2.6–3.8	2001	18
IL Test (Instrumentation Laboratories, Fisher Scientific, Unionville, Ontario, Canada)	49–109 to 63–101	1.7–3.8 to 1.9–3.3	2001	18
Thrombosis I (Ortho Diagnostic Systems, Raritan, New Jersey)	44–75 to 58–112	1.6–2.7 to 2.4–4.5	2001	18

* aPTT = activated partial thromboplastin time.

Table 2. Some Aspects of Unfractionated Heparin Monitoring, Unfractionated Heparin Dose Adjustment, and Clinical Outcomes in Reviewed Studies*

Study (Reference)	Sites	Patients	aPTT Therapeutic Range	Range Validated	Steady-State Unfractionated Heparin Dosage
	<i>n</i>				<i>U/d</i>
Belcaro et al. (1)	3	294	60–85 s	Yes	NR
Breddin et al. (2)	71	2607	1.5–2.5 times control	No	NR
The Columbus Investigators (3)	31	1021	1.5–2.5 times control	No	28 600
Duroux (4)	20	166	1.5–2.0 times control	No	34 225
Fiessinger et al. (5)	16	80	1.5–3.0 times control	No	26 300
Harenberg et al. (6)	29	538	2.0–3.0 times control	No	34 200
Hull et al. (7)	15	432	1.5–2.5 times control	No	NR
Koopman et al. (8)	9	400	1.5–2.0 times control	Yes	27 800
Levine et al. (9)	15	500	60–85 s	Yes	NR
Lindmarker et al. (10)	5	204	1.5–3.0 times control	No	25 400
Luomanmäki et al. (11)	7	330	1.5–3.0 times control	No	27 300
Merli et al. (12)	74	900	55–80 s	No	29 050
Prandoni et al. (13)	2	170	1.5–2.0 times control	No	33 000
Simonneau et al. (14)	6	134	1.5–2.5 times control	No	NR
Simonneau et al. (15)	11	612	2.0–3.0 times control	No	27 500

* aPTT = activated partial thromboplastin time; DVT = deep venous thrombosis; INR = international normalized ratio; LMWH = low-molecular-weight heparin; NR = not reported; PE = pulmonary embolism.

sites—analogue to using an international normalized ratio to interpret prothrombin time results. However, it is unclear whether these three studies actually used the recommended procedure, since they used a single aPTT therapeutic range at multiple sites. Such an approach would not be valid unless the same thromboplastin reagent, reagent lot, and coagulometer were used in every contributing site.

Most of the clinical trials we reviewed considered an aPTT ratio of 1.5 times the control value as therapeutic. Yet when we reviewed reports published over the last 20 years, we could not find a single aPTT reagent that produced aPTT results as low as 1.5 times the control value in response to therapeutic heparin levels. Examples from a few of the studies included in that review appear in Table 1. An aPTT of 2.0 to 3.5 times the control value is required to achieve therapeutic heparin levels for most modern aPTT reagents (19).

Unfortunately, the recommended method for establishing a therapeutic range for aPTT reagents is onerous and beyond the capacity of many laboratories. The laboratory in question is required to collect plasma samples from approximately 30 patients receiving heparin and to perform simultaneous aPTT and heparin levels (by factor Xa inhibition or protamine titration) (18). Linear regression is then used to calculate the aPTT range that correlates with heparin levels of 0.3 to 0.7 IU/mL by factor Xa inhibition or 0.2 to 0.4 IU/mL by protamine titration. In almost all cases, the resulting validated therapeutic aPTT range will be higher than 1.5 to 2.5 times the control value. The efficacy and safety of unfractionated heparin are likely to be compromised at clinical sites that fail to calibrate their aPTT method in the recommended manner.

We conclude that in most of the clinical trials com-

paring unfractionated heparin with LMWH in treating patients with venous thromboembolism, the effectiveness of unfractionated heparin could have been compromised because of suboptimal unfractionated heparin monitoring and dosing. Because of limitations of the available data, we could not demonstrate that suboptimal dosing and monitoring were associated with worse clinical outcomes. However, the results of our analysis suggest that the apparent inferiority of unfractionated heparin to LMWH reported in meta-analyses could be the result of suboptimal dosing of unfractionated heparin. This observation does not detract from other important advantages of LMWH. Unfractionated heparin is difficult to monitor and dose in an optimal manner. In contrast, LMWH does not require laboratory monitoring and is effective and safe when given as a once-daily subcutaneous injection.

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References

- Belcaro G, Nicolaidis AN, Cesarone MR, Laurora G, De Sanctis MT, Incandela L, et al. Comparison of low-molecular-weight heparin, administered primarily at home, with unfractionated heparin, administered in hospital, and subcutaneous heparin, administered at home for deep-vein thrombosis. *Angiology*. 1999;50:781-7. [PMID: 10535716]
- Breddin HK, Hach-Wunderle V, Nakov R, Kakkar VV. Effects of a low-

Table 2—Continued

DVT or PE				Major Bleeding			
Rate in LMWH Group	Rate in Unfractionated Heparin Group	Difference (95% CI)	P Value	Rate in LMWH Group	Rate in Unfractionated Heparin Group	Difference (95% CI)	P Value
%		percentage points		%		percentage points	
6.1	6.2	-0.1 (NR)	NR	0	0	0 (NR)	NR
1.8	6.4	-4.6 (-7.8 to -1.4)	NR	0.3	1.5	-1.2 (NR)	NR
5.3	4.9	0.4 (NR)	NR	3.1	2.3	0.8 (NR)	0.63
3.8	2.8	1.0 (NR)	NR	2.3	5.0	-2.7 (NR)	0.40
4.5	2.5	2.0 (NR)	NR	0	1.5	-1.5 (NR)	NR
2.3	5.5	-3.2 (NR)	0.07	1.5	4.0	-2.5 (NR)	0.11
2.8	6.9	-4.1 (NR)	NR	0.5	5.0	-4.5 (NR)	0.006
6.9	8.6	-1.7 (-6.9 to 3.6)	NR	0.5	2.0	-1.5 (-0.7 to 2.7)	NR
5.3	6.7	-1.4 (-5.7 to 3.0)	NR	2.0	1.2	0.8 (NR)	0.50
5.0	3.0	2.0 (NR)	NR	0	0	0 (NR)	NR
5.0	3.0	2.0 (NR)	NR	0	0.7	-0.7 (NR)	NR
2.9	4.1	-1.2 (-4.2 to 1.7)	NR	1.3	2.1	-0.8 (-2.9 to 3.0)	NR
7.0	14.0	-7.0 (-15.0 to 3.0)	NR	1.1	3.5	-2.4 (-5.0 to 3.0)	NR
0	4.5	-4.5 (NR)	NR	0	0	0 (NR)	NR
1.6	1.9	-0.3 (-2.4 to 1.8)	NR	2.0	2.6	-0.6 (-3.0 to 1.8)	NR

molecular-weight heparin on thrombus regression and recurrent thromboembolism in patients with deep-vein thrombosis. *N Engl J Med.* 2001;344:626-31. [PMID: 11228276]

3. Low-molecular-weight heparin in the treatment of patients with venous thromboembolism. The Columbus Investigators. *N Engl J Med.* 1997;337:657-62. [PMID: 9280815]

4. A randomised trial of subcutaneous low molecular weight heparin (CY 216) compared with intravenous unfractionated heparin in the treatment of deep vein thrombosis. A collaborative European multicentre study. *Thromb Haemost.* 1991;65:251-6. [PMID: 1646490]

5. Fiessinger JN, Lopez-Fernandez M, Gatterer E, Granqvist S, Kher A, Olsson CG, et al. Once-daily subcutaneous dalteparin, a low molecular weight heparin, for the initial treatment of acute deep vein thrombosis. *Thromb Haemost.* 1996;76:195-9. [PMID: 8865530]

6. Harenberg J, Schmidt JA, Koppenhagen K, Tolle A, Huisman MV, Büller HR. Fixed-dose, body weight-independent subcutaneous LMW heparin versus adjusted dose unfractionated intravenous heparin in the initial treatment of proximal venous thrombosis. EASTERN Investigators. *Thromb Haemost.* 2000;83:652-6. [PMID: 10823256]

7. Hull RD, Raskob GE, Pineo GF, Green D, Trowbridge AA, Elliott CG, et al. Subcutaneous low-molecular-weight heparin compared with continuous intravenous heparin in the treatment of proximal-vein thrombosis. *N Engl J Med.* 1992;326:975-82. [PMID: 1545850]

8. Koopman MM, Prandoni P, Piovello F, Ockelford PA, Brandjes DP, van der Meer J, et al. Treatment of venous thrombosis with intravenous unfractionated heparin administered in the hospital as compared with subcutaneous low-molecular-weight heparin administered at home. The Tasman Study Group. *N Engl J Med.* 1996;334:682-7. [PMID: 8594426]

9. Levine M, Gent M, Hirsh J, Leclerc J, Anderson D, Weitz J, et al. A comparison of low-molecular-weight heparin administered primarily at home with unfractionated heparin administered in the hospital for proximal deep-vein thrombosis. *N Engl J Med.* 1996;334:677-81. [PMID: 8594425]

10. Lindmarker P, Holmström M, Granqvist S, Johnsson H, Lockner D. Comparison of once-daily subcutaneous Fragmin with continuous intravenous unfractionated heparin in the treatment of deep vein thrombosis. *Thromb Haemost.* 1994;72:186-90. [PMID: 7831649]

11. Luomanmäki K, Granqvist S, Hallert C, Jauro I, Ketola K, Kim HC, et al. A multicentre comparison of once-daily subcutaneous dalteparin (low molecular weight heparin) and continuous intravenous heparin in the treatment of deep

vein thrombosis. *J Intern Med.* 1996;240:85-92. [PMID: 8810934]

12. Merli G, Spiro TE, Olsson CG, Abildgaard U, Davidson BL, Eldor A, et al. Subcutaneous enoxaparin once or twice daily compared with intravenous unfractionated heparin for treatment of venous thromboembolic disease. *Ann Intern Med.* 2001;134:191-202. [PMID: 11177331]

13. Prandoni P, Lensing AW, Büller HR, Carta M, Cogo A, Vigo M, et al. Comparison of subcutaneous low-molecular-weight heparin with intravenous standard heparin in proximal deep-vein thrombosis. *Lancet.* 1992;339:441-5. [PMID: 1346817]

14. Simonneau G, Charbonnier B, Decousus H, Planchon B, Ninet J, Sie P, et al. Subcutaneous low-molecular-weight heparin compared with continuous intravenous unfractionated heparin in the treatment of proximal deep vein thrombosis. *Arch Intern Med.* 1993;153:1541-6. [PMID: 8391792]

15. Simonneau G, Sors H, Charbonnier B, Page Y, Laaban JP, Azarian R, et al. A comparison of low-molecular-weight heparin with unfractionated heparin for acute pulmonary embolism. The THESEE Study Group. *Tinzaparine ou Heparine Standard: Evaluations dans l'Embolie Pulmonaire.* *N Engl J Med.* 1997;337:663-9. [PMID: 9278462]

16. Lensing AW, Prins MH, Davidson BL, Hirsh J. Treatment of deep venous thrombosis with low-molecular-weight heparins. A meta-analysis. *Arch Intern Med.* 1995;155:601-7. [PMID: 7887755]

17. Rocha E, Martínez-González MA, Montes R, Panizo C. Do the low molecular weight heparins improve efficacy and safety of the treatment of deep venous thrombosis? A meta-analysis. *Haematologica.* 2000;85:935-42. [PMID: 10980632]

18. Brill-Edwards P, Ginsberg JS, Johnston M, Hirsh J. Establishing a therapeutic range for heparin therapy. *Ann Intern Med.* 1993;119:104-9. [PMID: 8512158]

19. Bates SM, Weitz JI, Johnston M, Hirsh J, Ginsberg JS. Use of a fixed activated partial thromboplastin time ratio to establish a therapeutic range for unfractionated heparin. *Arch Intern Med.* 2001;161:385-91. [PMID: 11176764]

20. Olson JD, Arkin CF, Brandt JT, Cunningham MT, Giles A, Koepke JA, et al. College of American Pathologists Conference XXXI on laboratory monitoring of anticoagulant therapy: laboratory monitoring of unfractionated heparin therapy. *Arch Pathol Lab Med.* 1998;122:782-98. [PMID: 9740136]

21. Hyers TM, Agnelli G, Hull RD, Morris TA, Samama M, Tapson V, et al. Antithrombotic therapy for venous thromboembolic disease. *Chest.* 2001;119:176S-193S. [PMID: 11157648]