ARTICLE

Evaluation of 2 Weight-Based Protocols for Administration of Heparin

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ABSTRACT

Background: In 1996, a weight-based protocol for administration of heparin was implemented and assessed at the authors' institution. Since then, several modifications have been made, including introduction of a lower-target protocol. These changes warranted re-evaluation of the standard and lower-target protocols.

Objective: To determine and compare the efficacy and safety of the standard and lower-target protocols for heparin administration and to descriptively compare these findings with the original 1996 protocol.

Methods: This 5-month retrospective, observational study involved 100 consecutive patients, 50 assigned to each of the 2 current protocols (standard and lower target), who were treated between September 2006 and January 2007. The primary outcomes were efficacy, represented by the time to achieve partial thromboplastin time (PTT) above the lower limit of the therapeutic range and within the therapeutic range, and safety, as indicated by the incidence of major bleeding and thromboembolic events over the entire course of heparin therapy.

Results: There were no significant differences between the standard and lower-target protocols with respect to median time to achieve PTT above the lower limit of the therapeutic range (6.0 h versus 6.3 h, respectively; $p = 0.24$) or median time to achieve PTT within the therapeutic range (14.4 h versus 14.3 h, respectively; $p = 0.93$). Compared with the original 1996 protocol, these protocols appeared to have shorter times to achieve both of these outcomes. The rate of adverse events was infrequent, with fewer episodes of major bleeding (1%, for both current protocols combined) than in the 1996 study (10%).

Conclusions: The 2 current weight-based protocols for administration of heparin appeared to have similar efficacy and safety and appeared to perform at least as well as the original 1996 protocol.

Key words: heparin, protocol, nomogram, venous thromboembolism, acute coronary syndrome

RÉSUMÉ

Contexte : En 1996, un protocole d'administration de l'héparine fondée sur le poids a été mis en œuvre et évalué à l'établissement des auteurs. Depuis, plusieurs modifications ont été apportées, y compris l'introduction d'un protocole à valeurs cibles inférieures. Ces changements ont commandé la réévaluation des deux protocoles d'administration d'héparine.

Objectif : Déterminer et comparer l'efficacité et l'innocuité des protocoles standard et à valeurs cibles inférieures pour l'administration d'héparine et présenter une comparaison descriptive des résultats obtenus à ceux du protocole original de 1996.

Méthodes : Cette étude d'observation rétrospective de cinq mois a été menée chez 100 patients traités consécutivement entre septembre 2006 et janvier 2007, 50 étant assignés à chacun des deux protocoles (standard et valeurs cibles inférieures). Les paramètres d'évaluation primaires étaient l'efficacité, représentée par le temps écoulé pour obtenir un temps partiel de thromboplastine (PTT) au-dessus de la limite inférieure de l'écart thérapeutique et à l'intérieur de l'écart thérapeutique, et l'innocuité, selon l'incidence de saignements importants et d'événements thromboemboliques pendant toute la durée de l'héparinothérapie.

Résultats : Les protocoles standard et à valeurs cibles ne différaient pas significativement quant au temps médian écoulé pour obtenir un PTT au-dessus de la limite inférieure de l'écart thérapeutique (respectivement 6,0 heures contre 6,3 heures, $p = 0,24$) ou quant au temps médian pour obtenir un PTT à l'intérieur de l'écart thérapeutique (respectivement 14,4 heures contre 14,3 heures, $p = 0,93$). Ces protocoles semblaient requérir moins de temps pour satisfaire à ces deux paramètres d'évaluation que dans l'étude de 1996. Les effets indésirables étaient peu fréquents, avec un taux de saignements importants (1 %, pour les deux protocoles actuels réunis) moindre que dans l'étude de 1996 (10 %).

Conclusions : Les deux protocoles actuels d'administration d'héparine fondés sur le poids semblent être aussi sûrs et efficaces que le protocole original de 1996.

Mots clés : héparine, protocole, nomogramme, thromboembolie veineuse, syndrome coronarien aigu

[Traduction par l'éditeur]

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INTRODUCTION

In recent years, significant focus has been placed on establishing weight-based protocols for administration of heparin to optimize patient outcomes in the treatment and prevention of conditions such as deep vein thrombosis, pulmonary embolism, and acute coronary syndrome.[1-10] In 1996, the authors' hospital developed a weight-based heparin protocol. A formal assessment revealed that, relative to traditional non-weight-based dosing, the weight-based protocol was superior in terms of the time required to achieve a minimum level of therapeutic anticoagulation, without an increase in adverse events.[1]

Over the subsequent 10 years, several modifications were introduced to the original weight-based protocol, which had been accepted as standard of practice since its initial evaluation.[1] These modifications were (1) determination of the therapeutic range of partial thromboplastin time (PTT) on the basis of anti-Xa units per millilitre, rather than a range based on PTT levels 1.5–2.5 times above baseline; (2) changes to the incremental adjustments in heparin dose for patients with supratherapeutic and subtherapeutic PTT; (3) use of newer, more sensitive reagents for laboratory assessment of PTT levels; and (4) introduction of a protocol with a lower target PTT in August 2006. As a result, physicians now have a choice between 2 weight-based heparin protocols. The standard heparin protocol (Appendix 1), which is analogous to the original 1996 protocol, is intended for patients with active thromboembolic disease. It targets anti-Xa levels of 0.3–0.7 units/mL,[11] corresponding to therapeutic PTT values of 70–130 s. The lower-target protocol (Appendix 2) replaced a previously existing protocol that was used in the hospital's cardiac care unit. Its application was expanded to include patients with acute coronary syndrome or neurologic indications for anticoagulation (e.g., stroke) and early postsurgical patients who require anticoagulation but who have no active deep vein thrombosis, pulmonary embolism, or peripheral arterial thrombosis. This protocol targets anti-Xa levels of 0.2–0.5 units/mL, corresponding to a PTT range of 60–100 s. This lower anti-Xa range has been recommended for the treatment of acute myocardial infarction[12] and is achieved by using a lower initial bolus dose (70 units/kg to a maximum of 5000 units, rather than 75–100 units/kg to a maximum of 9000 units in the standard protocol), as well as lower initial maintenance doses.

The heparin protocol used in the cardiac care unit, which formed the basis of the lower-target protocol, had never been formally evaluated, and the standard heparin protocol had been substantially revised since its initial analysis. Therefore, the objective of this study was to determine and compare the efficacy and safety of the two 2006 heparin protocols and to descriptively compare these results to the results of the original 1996 study.[1]

METHODS

A retrospective, open-label observational study was conducted over a period of 5 months (September 2006 to January 2007). Approval to conduct this study was obtained from the University of British Columbia Clinical Research Ethics Board and the Vancouver Coastal Health Research Institute. The 2 current protocols were implemented in August 2006. The decision as to which protocol would be appropriate for an individual patient was left to the discretion of the physician, on the basis of the clinical indication. Patients to be included in the study were identified from a drug report generated daily by the pharmacy computer system. The goal was to enrol a convenience sample of 50 patients for whom the standard protocol (Appendix 1) was used and 50 patients for whom the lower-target protocol (Appendix 2) was used, independent of indication. Patients were excluded if they had received heparin for less than 24 h or if there had been any deliberate, documented changes in the heparin protocols, other than omitting the bolus dose (e.g., changes in target PTT range specified in writing by the physician).

PTT was monitored for the first 48 h of continuous IV infusion of heparin (or longer if the therapeutic target was not achieved within 48 h). The time to the first PTT measurement and the corresponding PTT value, the time to reach PTT above the lower limit of the therapeutic range, and the time to achieve PTT within the therapeutic range were collected from each patient's chart. The percentage of patients who had reached the therapeutic range at any point within the first 24 h was also determined. If the initial PTT value was above 200 s (the limit of detection for PTT measurement), the number of adjustments to the rate of heparin infusion required to lower the PTT to within the therapeutic range within the first 48 h was documented. In order for the first PTT value to be included in the efficacy analysis, it had to be measured at least 4 h and less than 8 h after initiation of heparin therapy. The indication for heparin therapy, the duration of therapy, and the appropriateness of choice of protocol were also collected.

For all patients included in the study, PTT was determined using the STA-PTT Automate 5 activated PTT reagent, with interpretation by the STA-R Evolution coagulation analyzer (Diagnostica Stago, Asnières, France). The PTT range was determined by the hematopathology department at the authors' hospital site, on the basis of anti-Xa levels obtained from a series of patient samples. These values were graphed on the x axis against the patients' PTT levels to generate a regression line, which allowed ascertainment of PTT values at various anti-Xa levels (C. Carter, MD, FRCPC, hematopathologist, Vancouver General Hospital, personal communication by email, October 15, 2008).

Adverse events were assessed for the entire course of heparin therapy. Major bleeding was defined as overt bleeding with one or more of the following: a decrease in hemoglobin of 20 g/L, transfusion of 2 or more units of blood, and hemorrhage in the retroperitoneum, the cranium, or a prosthetic joint.[1,3] The PTT at the time of bleeding was also recorded. Recurrence of deep vein thrombosis or pulmonary embolism was determined on the basis of radiographic confirmation or high clinical suspicion. The cause of death was documented for patients who died while receiving heparin therapy.

Compliance with the heparin protocol was evaluated for the first 48 h of therapy. Information in the patients' charts was assessed for the following protocol violations: errors in the bolus dose, incorrect adjustments to the rate of maintenance infusion, incorrect infusion hold time for patients with high PTT values, incorrect sampling time for initial PTT (defined as first PTT sample drawn more than 2 h before or after the scheduled time), omission of PTT documentation, omission of a coagulation test, or failure of nursing staff to contact the physician after 3 consecutive subtherapeutic or supratherapeutic PTT values.

The primary efficacy outcomes were the time to achieve PTT above the lower limit of the therapeutic range and within the therapeutic range. The primary safety outcomes were the incidence of major bleeding and recurrence of deep vein thrombosis or pulmonary embolism. The secondary outcome measures were the total number and types of protocol violations and their associated effects on the primary efficacy outcomes.

A convenience sample size of 50 patients for each heparin protocol was chosen to match the sample size of the 1996 study.[1] Summary descriptive and inferential statistics were obtained using SPSS 15.0, with means and standard deviations reported for normally distributed data and medians and ranges for nonparametric data. The efficacy outcomes of the two 2006 heparin protocols were analyzed and compared using the Mann–Whitney *U* test for nonparametric data. The level of significance was set at $p < 0.05$. Because the original data for the 1996 study were irretrievable, summary means and standard deviations were used to qualitatively compare the 2006 and 1996 protocols.

RESULTS

Charts were reviewed for a total of 153 consecutive patients who had a prescription for heparin infusion. Fifty-three patients were excluded for the following reasons: total infusion time less than 24 h ($n = 23$), heparin protocol not used ($n = 9$), older version of protocol used ($n = 5$), heparin infusion started at another hospital ($n = 4$), protocol modified by physician ($n = 4$), incorrect initial infusion rate ($n = 2$), switch in protocols during therapy ($n = 2$), interruption in heparin therapy before first PTT sample was drawn ($n = 1$), and inadvertent exclusion ($n = 3$). This left a total of 100 patients with 50 patients in each group.

In the 1996 study, almost all patients received a full bolus dose of heparin; however, in the current study, only two-thirds of patients in the standard 2006 protocol group and only about half of those in the lower-target protocol group received a full bolus (Table 1). The standard protocol was ordered appropriately for the majority of patients in the current study (88%) (Table 1); the exceptions were 6 patients who received heparin according to this protocol for treatment of acute coronary syndrome. These 6 patients were receiving care on a nursing unit that did not have preprinted orders for the lower-target protocol; the forms have since been made available on this nursing unit. The lower-target protocol was ordered inappropriately for 5 patients, 3 with active venous thromboembolic disease and 2 with peripheral arterial thrombosis.

Overall, there were no statistically significant differences between the two 2006 protocols with respect to times to achieve PTT above the lower limit and within the therapeutic range (Table 2). The times to achieve these outcomes appeared shorter for the current protocols than for the original 1996 protocol (Table 2). Two values for patients treated with the standard protocol were excluded from the analysis of time to achieve PTT value above the lower limit of the target range. The samples for these initial PTTs were drawn late, at 12 and 14 h after initiation of heparin, respectively. Similarly, 3 values for patients treated with the lower-target protocol were excluded because the PTT samples were drawn too early, at less than 4 h after initiation. Of note, for one patient who was receiving heparin via the standard protocol, the PTT remained slightly above the therapeutic range (134 s) at 48 h after initiation, and an arbitrary time of 54 h was assigned to achieve the target. This extension was applied because the heparin dose had been reduced per protocol at 48 h, but the infusion was then discontinued before the next scheduled PTT measurement could be obtained, 6 h later. It was anticipated that if the heparin infusion had been continued, the PTT would have been within target range by the next measurement.

There was no statistically significant difference between the standard and lower-target protocol groups for time to the first PTT measurement, and for both of these groups the value for this outcome appeared similar to that in the 1996 study (Table 2). About one-third of patients in both of the 2006 protocol groups had achieved therapeutic PTT levels by the time of the first measurement, and about half of the initial PTT values in both groups were supratherapeutic. In the 1996 study, about two-thirds of initial PTT values were supratherapeutic. The majority of patients in the current study had at least one PTT value above the lower limit of the therapeutic range and within the target range by 24 h. Of the 16 patients in the

Table 1. Demographic Characteristics of Patients at Baseline

Characteristic	Protocol; No. (%) of Patients or Mean ± SD		
	2006 Standard Protocol*	2006 Lower-Target Protocol†	1996 Study[1]‡
No. of patients	50 (100)	50 (100)	50 (100)
Full bolus	33 (66)	26 (52)	47 (94)
Half bolus	0	4 (8)	Unknown§
No bolus	17 (34)	20 (40)	Unknown§
Age (years)	66.3 ± 15.0	70.1 ± 13.4	58.0 ± 17.2
Weight (kg)	77.7 ± 21.7	73.6 ± 17.0	76.1 ± 17.9
Sex, males	29 (58)	29 (58)	24 (48)
Indication			
Acute coronary syndrome	6 (12)	32 (64)	0
DVT or PE	34 (68)	3 (6)	50 (100)
Peripheral arterial thrombosis	4 (8)	2 (4)	0
Bridging for warfarin therapy	4 (8)	2 (4)	0
Atrial fibrillation	2 (4)	6 (12)	0
Transient ischemic attack or stroke	0	4 (8)	0
Thrombophlebitis	0	1 (2)	0
Protocol appropriate	44 (88)	45 (90)	NA
Baseline PTT (s)	40 ± 9	39 ± 8	25.3 ± 2.7
Baseline platelet count × 10^9/L	258 ± 114	216 ± 125	289 ± 142
Duration of heparin therapy (days)	5.5 ± 7.2	6.3 ± 9.1	6.2 ± 4.2

DVT = deep vein thrombosis, NA = not applicable, PE = pulmonary embolism, PTT = partial thromboplastin time, SD = standard deviation.
*PTT target 70–130 s.
†PTT target 60–120 s.
‡PTT target 46–70 s.
§Report did not specify whether remaining 3 patients received half bolus or no bolus.

standard protocol group with an initial PTT value above 200 s (the upper limit of detection), most required at least 2 adjustments of the heparin infusion rate to reach PTT values within the therapeutic range (range 1 to 3). Patients in the lower-target protocol group required fewer rate adjustments: 3 of the 6 patients with initial PTTs above 200 s required only 1 rate adjustment, and 3 required 2 rate adjustments.

In both of the 2006 protocol groups, there was no statistical difference in the median time to achieve PTT above the lower limit of the target range between patients who received a full bolus dose and those who did not receive a full bolus (standard protocol 6.0 h [4.0–24.0 h] versus 6.0 h [4.0–40.8 h], $p = 0.41$; lower-target protocol 6.0 h [4.5–14.3 h] versus 6.9 h [4.8–39.5 h], $p = 0.12$). Similar results were observed for the median time to achieve PTT within the therapeutic range (standard protocol 13.8 h [4.0–36.3 h] versus 21.5 h [5.5–55.0 h], $p = 0.20$; lower-target protocol 14.4 h [4.5–24.5 h] versus 14.1 h [4.8–36.8 h], $p = 0.39$). Notably, the administration of a full bolus dose of heparin did not affect initial supratherapeutic PTTs (standard protocol 122 s [55–200 s] with bolus dose versus 132 s [46–200 s] with no bolus dose, $p = 0.72$; lower-target protocol 103 s [43–200 s] with bolus dose versus 80 s [52–200 s] with no bolus dose, $p = 0.17$).

Complete compliance with the protocols appeared higher in the current study than in the 1996 study[1]; nonetheless, protocol violations were documented for 29% of all patients in the current study (Table 3). Twenty errors were identified for 16 patients in the standard protocol group and 18 errors for 13 patients in the lower-target group; 49 errors were documented for 32 patients in the 1996 study.[1] The majority of errors were due to incorrect adjustments of the infusion rate and incorrect sampling times for initial PTT measurements. In general, patients with no protocol violations achieved the primary outcomes more quickly. In the standard protocol group, although there was no difference in time to achieve PTT above the lower limit, the time to achieve PTT within the therapeutic range was significantly shorter for patients with no protocol violations. In the lower-target protocol group, time to attain PTT above the lower limit was significantly shorter for patients with complete protocol compliance. However, for this group there was no statistical difference in time to achieve PTT within the target range whether or not there were protocol violations.

Adverse events were infrequent in the current study (Table 4). Only one major bleeding episode occurred in a patient in the lower-target protocol group. In the 1996 study, there were 5 episodes of major bleeding. A total of 3 deaths occurred in the current study, 2 in the standard protocol group and 1 in the lower-target protocol group. One of the deaths in the standard protocol group may have been due to treatment failure for

Table 2. Comparison of Selected Outcomes

Parameter	2006 Standard Protocol (*n* = 50)	2006 Lower-Target Protocol (*n* = 50)	1996 Study[1] (*n* = 50)
Primary outcomes			
Time to achieve PTT > lower limit of therapeutic range (h)			
Median (range)	6.0 (4.0–40.8)*	6.3 (4.5–53.0)*	
Mean ± SD	8.3 ± 6.8	9.7 ± 9.2	10.7 ± 11.1
Time to achieve PTT within therapeutic range (h)			
Median (range)	14.4 (4.0–40.8)†	14.3 (4.5–53.0)†	
Mean ± SD	17.2 ± 12.5	16.1 ± 10.5	22.3 ± 14.0
Other outcomes			
Time to first PTT measurement (h)			
Median (range)	6.0 (3.0–14.3)‡	6.0 (1.8–8)‡	
Mean ± SD	6.2 ± 1.6	6.0 ± 1.5	6.3 ± 1.1
Value of first PTT (s)			
Median (range)	128 (53–200)	88 (43–200)	
Mean ± SD	137 ± 56	106 ± 49	NA
First PTT therapeutic (no. and % of patients)	18 (36)	18 (36)	NA
First PTT subtherapeutic (no. and % of patients)	7 (14)	10 (20)	NA
First PTT supratherapeutic (no. and % of patients)	25 (50)	22 (44)	31 (62)
Value of first supratherapeutic PTT (s)			
Median (range)§	200 (132–200)	150 (101–200)	
Mean ± SD	188 ± 23	152 ± 37	118.9 ± 28.9
PTT within 24 h (no. and % of patients)			
Patients with PTT > lower limit of therapeutic range	48 (96)	47 (94)	NA (80.9)
Patients with PTT within therapeutic range	40 (80)	40 (80)	NA
Patients with rate adjustments to therapeutic range if initial PTT > 200 s			
1 adjustment	3/16	3/6	NA
2 adjustments	7/16	3/6	NA
> 2 adjustments	6/16	0	NA

NA = not applicable or not available, PTT = partial thromboplastin time, SD = standard deviation.
*p = 0.24, for comparison between standard and lower-target protocols.
†p = 0.93, for comparison between standard and lower-target protocols.
‡p = 0.94, for comparison between standard and lower-target protocols.
§Limit of detection for PTT was 200 s; therefore, upper limit of ranges is given as 200 s, even though PTT was above 200 s for some patients.

pulmonary embolism, since the PTT was subtherapeutic for more than 30 h before the time of death. However, this patient had other serious comorbidities, including heart failure and pneumonia, which may have been contributing factors. The PTT in this patient was initially therapeutic, at 14 h after heparin initiation, but fell to 64 s by 22 h and remained subtherapeutic. Following the PTT measurement at 22 h, 2 protocol violations occurred: the heparin infusion rate was not increased and a sample for repeat PTT was not drawn for another 30 h, at which point the PTT remained subtherapeutic (60 s). At that point, the infusion rate was increased appropriately to reflect the measured PTT, but the patient died 6 h later. The second death in the standard protocol group involved a patient who died secondary to cardiac arrest. The third death (in the lower-target protocol group) occurred in a patient who fell 1 week after initiation of heparin for acute coronary syndrome. Heparin was continued for 2 days after the fall until an extensive right intralobar hemorrhagic stroke was discovered. The PTT at the time of this diagnosis was therapeutic (70 s) and heparin was neutralized with protamine. The patient died shortly thereafter. No arterial thromboembolic events were noted in this study. The 1996 study reported 2 cases of recurrent deep vein thrombosis or pulmonary embolism, and 3 deaths in total.[1] One of these deaths was due to recurrent deep vein thrombosis and/or pulmonary embolism, whereas the other 2 were not attributed to heparin therapy.

DISCUSSION

The results of this study suggest that the 2006 standard and lower-target weight-based heparin protocols used at the authors' institution were equally efficacious in achieving therapeutic PTT levels early in therapy, with comparable low incidences of adverse events. These protocols compared favourably to the original 1996 weight-based heparin protocol, which was evaluated previously.[1] Achieving anticoagulation early (within the first 24 h) after a thromboembolic event is critical to the optimization of patient outcomes.[3] Although the current protocols could not be compared by statistical testing with the 1996 protocol, there appeared to be greater percentages of patients with PTT values above the lower limit of the target range within 24 h in both the standard and lower-target

Table 3. Protocol Violations

Violations and Effects	2006 Standard ` Protocol (*n* = 50)	2006 Lower Target Protocol (*n* = 50)	1996 Study[1] (*n* = 50)
No protocol violations (no. and % of patients)	34 (68)	37 (74)	18 (36)
Protocol violations (no. and % of violations)			
Total number of violations	20 18	49	
Incorrect adjustment of infusion rate	7 (35)	5 (28)	18 (37)
Incorrect sampling time for initial PTT	3 (15)	7 (39)	24 (49)*
Incorrect bolus dose	3 (15)	0	3 (6)
Incorrect infusion hold time	3 (15)	1 (6)	NA
Omission of documentation of PTT	2 (10)	0	NA
Omission of PTT test(s)	1 (5)	4 (22)	4 (8)
Physician not notified	1 (5)	1 (6)	0
Effect on primary outcomes (median and range)			
Time to PTT > lower limit of therapeutic range (h)			
For patients with no protocol violation	6.0 (4.0–26.5)†	6.3 (4.8–14.3)‡	NA
For patients with at least 1 protocol violation	6.0 (4.0–40.8)†	11.1 (5.5–53.0)‡	NA
Time to PTT within therapeutic range (h)			
For patients with no protocol violation	12.8 (4.0–55.0)§	14.0 (4.5–36.8)¶	NA
For patients with at least 1 protocol violation	22.0 (5.5–40.8)§	20.3 (6.0–53.0)¶	NA

NA = not applicable, PTT = partial thromboplastin time.
*For 1996 study, this value refers to incorrect sampling time for any PTT.
†$p = 0.59$, for comparison between group with no protocol violations and group with at least 1 protocol violation.
‡$p = 0.04$, for comparison between group with no protocol violations and group with at least 1 protocol violation
§$p = 0.017$, for comparison between group with no protocol violations and group with at least 1 protocol violation
¶$p = 0.08$, for comparison between group with no protocol violations and group with at least 1 protocol violation.

Table 4. Adverse Events

Event	Protocol; No. (%) of Patients*		
	2006 Standard Protocol (*n* = 50)	2006 Lower-Target Protocol (*n* = 50)	1996 Study[1] (*n* = 50)
Major bleeding episode	0	1 (2)	5 (10)
Recurrence of DVT or PE	0	0	2/43 (5)
Arterial thromboembolic disease	0	0	0
Death			
Due to major bleeding	0	1 (2)	0
Due to DVT or PE	1 (2)*	0	1 (2)
Other cause	1 (2)	0	2 (4)

DVT = deep vein thrombosis, PE = pulmonary embolism.
*Exact cause of death not confirmed.

protocol groups than in the 1996 analysis. As well, the time to achieve therapeutic anticoagulation for both of the 2006 protocols appeared shorter than for the 1996 protocol. With respect to safety, there was only 1 episode of major bleeding, which was induced by a fall. The rate of major bleeding in the current study (1%) was much lower than in the original study (10%) and was comparable to rates observed in recent clinical trials of patients treated with IV heparin for venous thromboembolism (less than 3%).[11]

Protocol compliance remained an issue, as it was in the 1996 study,[1] and violations of the protocol had a significant impact on the primary outcomes. The times to achieve PTT above the lower limit in the lower-target protocol group and within the therapeutic range in the standard protocol group were prolonged for patients with at least one protocol violation. Of note, the reported rates of compliance were likely underestimated, as compliance was assessed only during the first 48 h of therapy. Incorrect adjustments of the infusion rate and incorrect sampling times for PTT measurement were the major compliance errors observed. The importance of protocol adherence in achieving adequate anticoagulation and thus improving patient outcomes needs to be emphasized. To prevent these problems in the future, the findings of this study were reported in the local pharmacy newsletter,[13] which was distributed to various institutional sites in the region, targeting medical and nursing staff, as well as allied health care professionals.

Patients in the standard protocol group with initially supratherapeutic PTT values (above 200 s) required at least 2 or 3 adjustments to the infusion rate to reach the therapeutic range. For those in the lower-target group with initially supratherapeutic PTT, only 1 or 2 rate adjustments were necessary. The multiple adjustments required probably contributed to the lower percentage of patients who achieved

PTT values within the therapeutic range within 24 h relative to the percentage who achieved levels above the lower limit of therapeutic range (80% versus 94%–96%). Because of the risks of prolonged overanticoagulation, the standard protocol has been further modified since completion of the study reported here, with more aggressive dose reductions for patients with PTT values above the upper limit of detection (200 s): instead of reducing the infusion rate by 150 units/h (as shown in Appendices 1 and 2), the rate is reduced by 200 units/h in the new protocol. Even though potential overanticoagulation was not a concern for the lower-target protocol group, both of the 2006 protocols were changed in April 2007 for overall consistency.

IV heparin boluses are intended for immediate anticoagulation when infusion is initiated.[11] The findings of this study suggest that a heparin bolus may not affect the primary efficacy outcomes, nor does it contribute to initially supratherapeutic PTT values. While these observations are interesting, they are no more than hypothesis-generating, as this subgroup analysis was underpowered. As such, clinicians should continue with current dosing guidelines with respect to bolus doses.

The study reported here had several limitations. It might have been subject to the known biases of a retrospective analysis with nonprobability sampling, observational design, and comparison with historical controls. Although strict inclusion and exclusion criteria, standard study definitions, clear procedures for data collection, and objective study end points were used, reporting in the patients' health records may have been incomplete or inaccurate. This observational study was conducted over a relatively short period of time using a small convenience sample of 50 consecutive patients for each protocol, to correspond with the sample size in the 1996 study.[1] As well, the effects of heparin therapy were analyzed for only the first 48 h, and the initial efficacy of attaining therapeutic PTT must be balanced with the effectiveness, safety, and efficiency of the protocol for maintaining therapeutic PTT for the duration of therapy. This study was undertaken to replicate and allow comparison with the 1996 study; however, the individual patient data from the original study were irretrievable, and statistical comparisons could not be performed. Finally, the applicability of these findings to current practice may be limited. Almost 1 in 3 patients in this study had a protocol violation, and in January 2007, the laboratory changed its method of determining PTT (using less sensitive reagents), which has altered the therapeutic PTT ranges for both protocols. The heparin protocols were also modified shortly after completion of the study, as previously described, with more aggressive dose reductions for PTT values above the upper limit of detection.

In conclusion, the standard and lower-target heparin protocols implemented in August 2006 appeared equally efficacious and safe in achieving rapid therapeutic anticoagulation. Protocol violations significantly delayed the time to achieve therapeutic anticoagulation; reinforcement of protocol compliance is therefore critical to achieve rapid and safe anticoagulation.

References

1. Shalansky KF, FitzGerald JM, Sunderji R, Traboular SJ, O'Malley B, McCarron BI, et al. Comparison of a weight-based heparin nomogram with traditional heparin dosing to achieve therapeutic anticoagulation. *Pharmacotherapy* 1996;16(6):1076-1084.
2. Hull RD, Raskob GE, Hirsh J, Jay RM, Leclerc JR, Geerts WH, et al. Continuous intravenous heparin compared with intermittent subcutaneous heparin in the initial treatment of proximal-vein thrombosis. *N Engl J Med* 1986;315(18):1109-1114.
3. Raschke RA, Reilly BM, Guidry JR, Fontana JR, Srinivas S. The weight-based heparin dosing nomogram compared with a "standard care" nomogram. A randomized controlled trial. *Ann Intern Med* 1993;119(9): 874-881.
4. Gunnarsson PS, Sawyer WT, Montague D, Williams ML, Dupuis RE, Caiola SM. Appropriate use of heparin. Empiric vs nomogram-based dosing. *Arch Intern Med* 1995;155(5):526-532.
5. Raschke RA, Gollihare B, Peirce JC. The effectiveness of implementing the weight-based heparin nomogram as a practice guideline. *Arch Intern Med* 1996;156(15):1645-1649.
6. Becker RC, Ball SP, Eisenberg P, Borzak S, Held AC, Spencer F, et al. A randomized, multicenter trial of weight-adjusted intravenous heparin dose titration and point-of-care coagulation monitoring in hospitalized patients with active thromboembolic disease. Antithrombotic Therapy Consortium Investigators. *Am Heart J* 1999;137(1):59-71.
7. Brown G, Dodek P. An evaluation of empiric vs. nomogram-based dosing of heparin in an intensive care unit. *Crit Care Med* 1997;25(9):1534-1538.
8. Lackie CL, Luzier AB, Donovan JA, Feras HI, Forrest A. Weight-based heparin dosing: clinical response and resource utilization. *Clin Ther* 1998;20(4):699-710.
9. Stahl KL, Pollard DL. Redesign of a weight-based heparin protocol for improved outcomes in a community hospital. *J Nurs Care Qual* 2003; 18(3):193-201.
10. Zimmermann AT, Jeffries WS, McElroy H, Horowitz JD. Utility of a weight-based heparin nomogram for patients with acute coronary syndromes. *Intern Med J* 2003;33(1-2):18-25.
11. Hirsh J, Raschke R. Heparin and low-molecular-weight heparin: the Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy. *Chest* 2004;126(3 Suppl):188S-203S.
12. Menon V, Harrington RA, Hochman JS, Cannon CP, Goodman SD, Wilcox RG, et al. Thrombolysis and adjunctive therapy in acute myocardial infarction: the Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy. *Chest* 2004;126(3 Suppl):549S-575S.
13. Tsang D, Shalansky K, Lum E. Heparin protocol adherence. *Vancouver Coastal Health Drug Ther Newsl* 2007;14(3):3.

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Appendix 1. Heparin/warfarin standardized protocol. ©2006 Vancouver General Hospital. Reproduced by permission.

Date _____ **Time:** _____

1. Patient weight: _____kg.
2. No intramuscular injections.
3. If possible, avoid non-steroidal anti-inflammatory drugs (NSAIDs).
4. Laboratory: Baseline PTT, INR and CBC with platelet count
   CBC with platelet count on day 1, then every 2 days while on heparin
   INR daily when initiating warfarin
5. Discontinue previous heparin and low molecular weight heparin orders
6. a) **INITIAL HEPARIN THERAPY**
   Heparin IV bolus and initial infusion (using 25,000 units heparin/500 mL=50 units/mL) as below:

Patient Wt (kg)	**Heparin IV Bolus (units)**	**Initial Infusion**	
☐ less than or equal to 50	4,000	750 units/hour	= 15 mL/hour
☐ 51 to 60	5,000	1,000 units/hour	= 20 mL/hour
☐ 61 to 70	6,000	1,100 units/hour	= 22 mL/hour
☐ 71 to 90	7,000	1,300 units/hour	= 26 mL/hour
☐ 91 to 105	8,000	1,450 units/hour	= 29 mL/hour
☐ greater than 105	9,000	1,650 units/hour	= 33 mL/hour

   b) **PTT-ADJUSTED HEPARIN THERAPY**
   ‡PTT in 6 hours, then adjust heparin infusion and repeat PTT per sliding scale below:

*****CALL PHYSICIAN IF 3 CONSECUTIVE PTTs < 60 SEC OR > 160 SEC*****

PTT (sec)	**BOLUS DOSE IV**	**STOP INFUSION**	**RATE CHANGE (50 units/mL)**	**‡REPEAT PTT**
< 60	5,000	0	+3 mL/hour (increase by 150 units/hour)	6 hours
60 to 69	0	0	+2 mL/hour (increase by 100 units/hour)	6 hours
70 to 130 (Therapeutic)	0	0	(no change)	Next day
131 to 144	0	0	–1 mL/hour (decrease by 50 units/hour)	6 hours
145 to 160	0	30min	–2 mL/hour (decrease by 100 units/hour)	6 hours
> 160	0	60 min	–3 mL/hour (decrease by 150 units/hour)	6 hours

   ‡specify on lab requisition "STAT PTT"

7. **WARFARIN THERAPY**
   ☐ Warfarin _____ mg PO daily x 2 days to start on _____. (warfarin to be ordered on a daily basis thereafter)
8. Discontinue heparin after at least 5 days of combined heparin/warfarin therapy when INR greater than 2.0 for 2 consecutive days (physician order required).

PTT = partial thromboplastin time, INR = international normalized ratio, CBC = complete blood count.

Appendix 2. Lower-target heparin protocol: cardiac care unit, neurosciences, and surgery (for patients with no active deep vein thrombosis, pulmonary embolism, or peripheral arterial thrombosis).

Date _____ **Time:** _____

1. Patient weight: _____kg.
2. No intramuscular injections.
3. If possible, avoid non-steroidal anti-inflammatory drugs (NSAIDs).
4. Laboratory: Baseline PTT, INR and CBC with platelet count
   CBC with platelet count on day 1 then q2days while on heparin
5. a) **INITIAL HEPARIN THERAPY**
   Heparin bolus 70 units/kg: _____ units (maximum 5,000 units, round to nearest 500 units)
   (bolus not recommended in post-op patients if no active venous thromboembolic disease)

   Select initial infusion rate as per scheme outlined below (using 25,000 units heparin in 500 mL of IV fluid = 50 units/mL):

Patient Wt (kg)	**Initial Infusion**	
☐ less than or equal to 50	650 units/hour	= 13 mL/hour
☐ 51 to 60	750 units/hour	= 15 mL/hour
☐ 61 to 70	850 units/hour	= 17 mL/hour
☐ greater than 70	1,000 units/hour	= 20 mL/hour

   b) **PTT ADJUSTED HEPARIN THERAPY**
   PTT 6 hours after starting heparin, then continue to adjust heparin infusion and repeat PTT based on sliding scale below:

*****CALL PHYSICIAN IF 3 CONSECUTIVE PTTs < 50 SEC OR > 130 SEC*****

PTT(sec)	**BOLUS DOSE IV**	**INFUSION STOP**	**RATE CHANGE (50 units/mL)**	**REPEAT PTT**
<50	5,000	0	+3 mL/hour (increase by 150 units/hour)	6 hours
50 to 59	0	0	+2 mL/hour (increase by 100 units/hour)	6 hours
60 to 100 (Therapeutic)	0	0	0 (no change)	Next day
101 to 114	0	0	–1 mL/hour (dEcrease by 50 units/hour)	6 hours
115 to 130	0	30 min	–2 mL/hour (decrease by 100 units/hour)	6 hours
>130	0	60 min	–3 mL/hour (decrease by 150 units/hour)	6 hours

PTT = partial thromboplastin time, INR = international normalized ratio, CBC = complete blood count.