Netherlands
The Journal of Medicine

REVIEW

Monitoring of unfractionated heparin in critically ill patients

R. Aarab[1*], J. van Es[1], A.C.J.M. de Pont[2], M.B. Vroom[2], S. Middeldorp[1]

Department of [1]Vascular Medicine and [2]Intensive Care, Academic Medical Centre, University of Amsterdam, Amsterdam, the Netherlands, *corresponding author: tel.: +31 (0)20 5665976, fax: +31 (0)20 6968833, e-mail: r.aarab@amc.uva.nl

ABSTRACT

Background: In critically ill patients, dosing of unfractionated heparin (UFH) is difficult due to unpredictable pharmacokinetics, which has an impact on the time to reach therapeutic anticoagulation. We evaluated the quality of UFH therapy in critically ill patients in terms of activated partial thromboplastin time (APTT) test values and time to therapeutic range.

Methods: Patients admitted to the Intensive Care Unit (ICU) and Medium Care Unit (MCU) were screened for intravenous UFH administration. Time to therapeutic range was categorised into 0-12, 13-24 and >24 hours. APTT results were classified into categories of subtherapeutic, supratherapeutic and therapeutic tests. We identified to what extent the sub- and supratherapeutic values were aberrant of the limit of the therapeutic range (<5%, 5-15% and >15%).

Results: In 101 patients admitted to the ICU and MCU, time to therapeutic range was 24 hours in 56% of the population, whereas in 10% of the patients no therapeutic APTT was achieved during UFH treatment. Among the APTT levels, 29% of all test results measured in 24 hours were within the therapeutic range. Subtherapeutic values were found in 53% of the test results, of which 160/203 were more than 15% under the lower limit, whereas 18% of the test results were supratherapeutic, of which 40/69 more than 15% above the upper limit.

Conclusion: In this cohort of critically ill patients, therapeutic APTT values were reached within 24 hours in 56% of the patients. We conclude that intravenous UFH therapy can be improved in critically ill patients.

KEYWORDS

Activated partial thromboplastin time, unfractionated heparin, venous thromboembolism

INTRODUCTION

Anticoagulants are the cornerstone of treatment and secondary prevention of arterial and venous thromboembolism (VTE). Heparin was one of the first anticoagulants and is to date still extensively used for indications other than VTE, such as acute coronary syndrome (ACS), continuous dialysis techniques and various surgical procedures. Heparin catalyses the ability of the plasma protein antithrombin to inhibit the activity of thrombin, factor Xa, and factor IXa about 1000-fold.[1] There are two types of heparin with distinguishable pharmacological profiles that determine their use in clinical practice. Unfractionated heparin (UFH) can be administered by continuous intravenous infusion or – less commonly – by subcutaneous injection. The pharmacokinetics of UFH differ highly between individuals as well as within individuals over time, due to binding to various plasma proteins.[2] To establish a safe and optimal anticoagulant effect within a defined therapeutic range, close monitoring of UFH therapy is crucial. The activated partial thromboplastin time (APTT) is generally used for this purpose and its levels should be maintained between a predefined interval. An APTT level ranging from 1.5-2.5 times the baseline value is considered to be the optimal therapeutic range and has gained wide clinical acceptance. Low-molecular-weight heparin (LMWH) is a derivate of UFH, but has different and more favourable pharmacokinetics. Its superiority over UFH is documented by several trials for the treatment of VTE as well as for patients across the ACS spectrum in terms of fewer recurrent thrombotic events and myocardial infarction, respectively.[3-5] However, the magnitude of clinical benefit from LMWH is lower than estimated, as documented by cumulative evidence of 14 systematic reviews.[6] Twelve other studies involving 4971 patients treated with LMWH have shown an increased risk of major bleeding for those with a creatinine clearance <30 ml/min (OR 2.25, 95% CI

1.19-4.27).[7] Because patients with severe obesity or severe renal failure are often excluded from clinical trials, there are less data available for these populations. Consequently, because of the lack of evidence, UFH rather than LMWH is still often preferred in patients with an increased risk of bleeding, renal impairment or extreme obesity.

Too high and too low anticoagulant effects can be a serious threat in terms of either haemorrhage or ongoing thrombosis, respectively. Because of their severity of disease and altered metabolism, critically ill patients are particularly vulnerable for complications. The risk of overdosing in such cases may be intuitively lower with UFH compared with LMWH, and there is a perceived superior possibility to immediately reverse the anticoagulant effect.

In this pilot study we hypothesised that a stable and therapeutic APTT can be achieved within 24 hours with intravenous UFH in patients admitted to the Intensive Care Unit (ICU) and Medium Care Unit (MCU). An assessment of the quality of UFH treatment is made in terms of number of subtherapeutic, supratherapeutic and therapeutic APTT values.

MATERIAL AND METHODS

Study design and population

This is a retrospective cohort study involving data from the electronic medical records of patients admitted to the ICU and MCU. Due to the feasibility of data collection and analysis within the time frame that was allowed for this project, we aimed to include 100 patients.

We identified patients by performing a query in the laboratory database of patients in whom an APTT test was performed between January 2010 and December 2010. Inclusion was based on documentation of intravenous UFH therapy in the electronic general chart database (AZD). Further identification and exclusion went through the ICU patient data management system. As listed in the flowchart, exclusion criteria were non-therapeutic indications for UFH therapy, patients <18 years, UFH infusion for less than 24 hours or an interruption of infusion for 36 hours or more.

Data collection

We collected data from the electronic medical records including age, gender, weight and indication for anticoagulant therapy with UFH. Deep venous thrombosis (DVT) and pulmonary embolism (PE) were considered to be different manifestations of the same condition – venous thromboembolism (VTE) – and all other thrombotic events, such as sinus or abdominal thrombosis in either arterial or venous vessels were defined as 'other thrombotic events'. Patients receiving continuous veno-venous haemofiltration (CVVH) were reported.

For the current analysis, data are truncated at intervals of 0-12, 13-24 and >24 hours. The APTT results were classified into categories of subtherapeutic, supratherapeutic and therapeutic tests based on the individual therapeutic range. Furthermore, we identified to what extent the sub- and supratherapeutic values were aberrant of the lower or upper limit of the therapeutic range, respectively (<5%, 5-15% and >15%). The therapeutic APTT range in seconds was defined as set in the medical record by the treating physician before the start of infusion. When no individual therapeutic range was documented, we considered an APTT range of 1.5-2.0 times the upper normal value of 30 seconds as therapeutic (according to the local protocol of the AMC, Amsterdam, the Netherlands).

We also measured the number of patients in whom anticoagulation had to be discontinued, as well as the number of dose adjustments. We used the 'Dose adjustments/non-Therapeutic Test ratio' (DnTT ratio), defined as the number of dose adjustments in proportion to the number of non-therapeutic APTT levels during time of UFH infusion. The results are presented in the categories <1 and ≥1.

Finally, information on events such as (recurrent) thromboembolism and bleeding during UFH administration were collected. A bleeding event was defined as clinically overt bleeding in a critical location (intracranial, retroperitoneal, or pericardial), or bleeding leading to a decrease in haemoglobin level of 1 mmol/l or more, or leading to transfusion of two or more units of packed red blood cells.

Dosing regimen

The treating physician was allowed to determine the dosing regimen based on patient characteristics and clinical presentation. The target APTT level for each patient had to be set and documented in the electronic record. After an initial standard dose at a rate of 1000 units/hour, the treating physician had to evaluate whether a bolus of 1000-5000 units was indicated. Consensus was to measure the APTT four hours after the start of infusion; monitoring tests had to be performed at a six-hour interval, even when the APTT test value was within the therapeutic range.

Outcomes

The primary outcome was the time to achieve a therapeutic APTT level per patient (<12, <24 or >24 hours). The main secondary outcome was the percentage of subtherapeutic, supratherapeutic and therapeutic range of all APTT tests performed after UFH administration in time ranges as mentioned.

RESULTS

A total of 1906 patients in whom an APTT test was performed were screened for intravenous UFH administration. A total of 249 patients were eligible for the current analysis of whom 101 consecutive patients were included. The mean age was 66 years (range 23-88) and 40% were female. Main indications for UFH therapy were VTE (24%) and presence of a mechanical heart valve (23%). Clinical characteristics are listed in *table 1*.

The time to reach at least one therapeutic APTT test result is shown in *figure 1*. Overall, 56% of the patients achieved a therapeutic APTT within 24 hours and 24% were therapeutic in both 0-12 and 13-24 hours.

Table 1. *Baseline patient characteristics of the study population (n=101)*

Characteristic	
Age in years, median (range)	69 (23-88)
Female (%)	40
Weight in kg, median (range)	80 (35-120)
Receiving CVVH (%)	24
Indication for anticoagulant therapy, %	
VTE (DVT and/or PE)	24
Other locations thrombotic event (i.e. sinus/ abdominal)	11
Mechanical heart valve	23
Atrial fibrillation	16
ACS or cardiac ischaemia	13
IABP or Impella	5
Cardiac surgery	4
Other	5
Time of UFH infusion in hours, median (range)	86 (24-695)

kg= kilogram; CVVH= continuous veno-venous haemofiltration; VTE=venous thromboembolism; DVT = deep venous thrombosis; PE= pulmonary embolism; ACS=acute coronary syndrome; IABP=intra-aortic balloon pump.

Other outcomes are listed in *table 2*. Within 12 hours of UFH infusion, 20% of the APTT measurements were within the therapeutic range. Additionally, 58% and 22% consisted of sub- and supratherapeutic test results, respectively. Of the subtherapeutic APTT levels, 105/121 were more than 15% below the lower limit of the target;

Table 2. *Primary and secondary outcomes concerning (non) therapeutic APTT level*

Outcome	0-12 h	0-24 h	>24 h
Number of APTT tests performed after start of UFH infusion per patient, median (range)	2.0 (1-5)	4.0 (2-7)	9.0 (0-111)
Tests within time range, n (%)			
Total subtherapeutic	**121 (58)**	**203 (53)**	551(32)
Of which aberrant from the lower limit, n (%)			
≤5%	9 (7)	16 (8)	
5-15%	7 (6)	27 (13)	
>15%	105 (87)	160 (79)	
Therapeutic	**41 (20)**	**110 (29)**	
Total supratherapeutic	**45 (22)**	**69 (18)**	
Of which aberrant from the upper limit, n (%)			
≤5%	6 (13)	12 (17)	1008 (58)
5-15%	7 (16)	17 (25)	170 (10)
>15%	32 (71)	40 (58)	
Dose adjustments during time of UFH infusion, median (range)	**5 (0-34)**		
DnTT ratio <1, %	18		
DnTT ratio ≥1, %	78		
No dose adjustments, %	4		

APTT= activated partial thromboplastin time; UFH= unfractionated heparin; h=hours; n = number; DnTT= dose adjustments/non-therapeutic test ratio.

Figure 1. *Flowchart of study population*

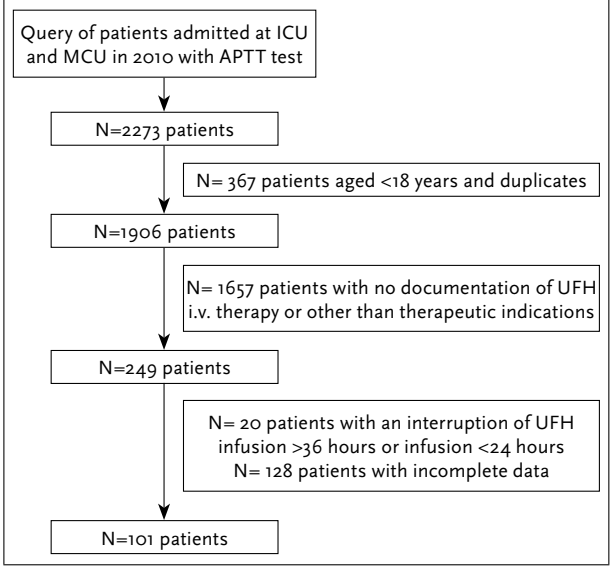
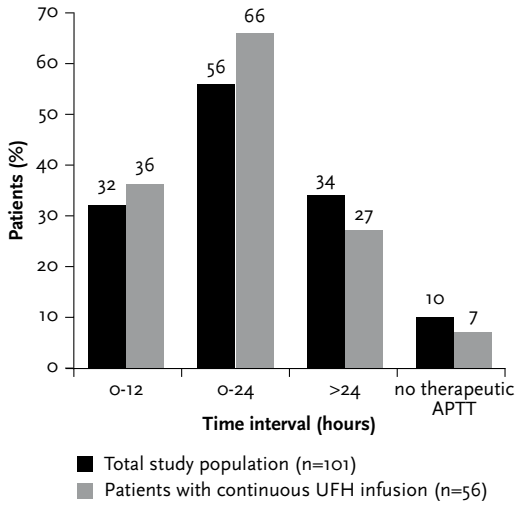


Figure 2. *Time to therapeutic range*



of the supratherapeutic levels, 32/45 were more than 15% above the upper limit of the target. Among the APTT levels measured at 24 hours, a therapeutic range was observed in 29% of the test results. Subtherapeutic values were found in 53% of the test results, of which 160/203 were more than 15% under the lower limit, whereas 18% of the test results were supratherapeutic, of which 40/69 more than 15% above the upper limit.

During the course of UFH therapy, ten patients had a bleeding event and six patients experienced a thrombotic event. The DnTT ratio was ≥1 in 78% of the study population.

In order to perform a medical procedure, UFH infusion was electively stopped in 44% of the cases. *Figure 1* shows that in the subpopulation (n=56) in which infusion remained continuous, 66% of the patients were therapeutically anticoagulated in 24 hours; the subtherapeutic, therapeutic and supratherapeutic rates were 51%, 33% and 15% respectively.

DISCUSSION

This cohort study demonstrates that among patients admitted to the ICU and MCU, achieving therapeutic heparinisation with UFH is challenging. Based on the time to therapeutic range being 24 hours for 56% of the study population and high percentages of subtherapeutic APTT results, we would expect a higher number of recurrent thrombotic events instead of bleeding. We identified ten patients in total in whom a bleeding event occurred; 4/10 patients had at least one supratherapeutic APTT level in 24 hours, and a small minority (12%) of all performed APTT tests were above the therapeutic range. We assume that other factors contributed to the bleeding events, independent of UFH therapy. Although an association between the incidence of bleeding and APTT values has been reported by subgroup analysis of large randomised trials, other investigators could not confirm similar results.[8-12]

However, there is evidence that failure to achieve therapeutic values within the first 24 hours is predictive of future recurrent VTE.[13] Research on patients with acute PE has also shown that reaching therapeutic anticoagulation within 24 hours lowers 30-day mortality and in-hospital mortality, which highlights the importance of rapid therapeutic anticoagulation.[14] To what extent rapid anticoagulation is achieved differs among trials which demonstrate therapeutic rates as low as 22%, while subanalysis of several studies found a significantly larger proportion of the patients reaching a therapeutic APTT level within 24 hours.[15-19] Whether these results apply for critically ill patients is uncertain, since these trials are not carried out in that specific patient category. We observed that in 56% of our study population, time to therapeutic range was 24 hours. It should be mentioned that the low therapeutic rates in our cohort could be due to the high percentage of patients who had a discontinuation of UFH infusion. We could not confirm whether an APTT was measured when the infusion was stopped, thus making the measured APTT not representative for UFH therapy. A subanalysis was therefore conducted which showed that in the subpopulation (n=56) treated with continuous UFH infusion, 66% achieved a therapeutic APTT within 24 hours, against 56% of the whole population (n=101). In terms of APTT test results in 24 hours, we noticed a small increase in therapeutic rates from 29% in the whole population to 33% in the subpopulation (n=56). Therefore, we conclude that APTT tests performed during discontinuation of UFH infusion are only to a small extent responsible for the low therapeutic rates in our cohort.

Conflicting observations between studies may have arisen from differences in protocols (e.g. fixed-dose versus weight-based regimen) or using different analytical techniques for determining UFH. Which approach concerning UFH therapy is superior is still inconclusive. For instance, there is considerable evidence that using weight combined with height and gender is more efficient for dosing UFH than weight alone.[15,20] But not all weight-based nomograms are consistent and they require a considerable amount of time for training healthcare professionals in their use in order to limit the potential for medication errors.[21] The American College of Chest Physicians (ACCP) therefore recommends – based on three available RCTs – a fixed-dose or a weight-adjusted regimen.[22]

Additionally, the APTT test itself is associated with significant intra- and inter-patient variability that is not related to circulating blood heparin activity or patient variables.[23-25] There is a lack of standardisation of methods since different reagents and instruments are used to perform an APTT test. To what extent the efficacy of UFH in general is dependent on (early) APTT test results is also uncertain.[26,27] An alternative for APTT would be monitoring the anti-Xa activity; its advantages have been discussed by several studies.[17,23] For example, a weight-based protocol in combination with the use of anti-Xa as monitoring technique results in a therapeutic heparinisation rate of 90% within 24 hours.[17,28] Despite the advantages, the anti-Xa assay is not widely incorporated in clinical use because of high costs and limited availability, whereas inter-laboratory variation still remains.[7,23,29]

Besides dosing regimens and laboratory instruments, the interpretation of the therapeutic range of the APTT levels might also play an important role in dosing UFH. A review performed by Raschke and colleagues included studies where different APTT reagents were used, so UFH

concentrations that were associated with a target APTT ratio of 1.5-2.5 times the control value, differed noticeably between trials.[30] Also, the clinical relevance of the fixed therapeutic range of 1.5-2.0 times the control APTT is uncertain and has not been confirmed by randomised trials.[7,31] Because of that and other methodological concerns, the ACCP recommends that the therapeutic APTT range at a particular laboratory should be adapted to responsiveness of the reagent and coagulometer used.[7]

Our study has several limitations. This analysis was designed as a pilot study, therefore the study sample was small. However, the included patients and clinical setting reflect real-life practice. Since the purpose of this survey was only to register the number of subtherapeutic, supratherapeutic and therapeutic APTT levels, we did not register the administered dose or infusion rate of UFH. The DnTT ratio was based on the total amount of dose adjustments per patient during time of infusion. Whether the dose is consecutively adjusted after a non-therapeutic APTT level is not represented. However, the DnTT ratio gives some indication of adherence to the dosing regimen; based on the ratio being ≥1 in 78% of the study population, we believe that the low therapeutic APTT rates are not the result of inadequate dose adjustment.

To conclude, time to therapeutic range was 24 hours in 56% of in total 101 patients admitted to the ICU and MCU. Of all obtained APTT results in 24 hours, 71% were sub- or supratherapeutic of which 200/272 were >15% aberrant from the therapeutic range. Therefore, intravenous UFH therapy can be improved in critically ill patients. More clinical trials are needed to examine optimal dosage regimens and to investigate the performance of other alternative anticoagulant therapies in critically ill patients.

ACKNOWLEDGEMENTS

The authors would like to thank Erik-Jan van den Dool of the clinical chemical laboratory of the Academic Medical Centre, Amsterdam, the Netherlands, for his expertise and help in offering the resources for this study.

REFERENCES

1. Middeldorp S. Heparin: from animal organ extract to designer drug. Thromb Res. 2008;122:753-62.
2. Hylek EM, Regan S, Henault LE, et al. Challenges to the effective use of unfractionated heparin in the hospitalized management of acute thrombosis. Arch Intern Med. 2003;163:621-7.
3. Murphy SA, Gibson CM, Morrow DA, et al. Efficacy and safety of the low-molecular weight heparin enoxaparin compared with unfractionated heparin across the acute coronary syndrome spectrum: a meta-analysis. Eur Heart J. 2007;28:2077-86.
4. Quinlan DJ, McQuillan A, Eikelboom JW. Low-molecular-weight heparin compared with intravenous unfractionated heparin for treatment of pulmonary embolism: a meta-analysis of randomized, controlled trials. Ann Intern Med. 2004;140:175-83.
5. van Dongen CJ, van den Belt AG, Prins MH, Lensing AW. Fixed dose subcutaneous low molecular weight heparins versus adjusted dose unfractionated heparin for venous thromboembolism. Cochrane Database Syst Rev. 2004;(4):CD001100.
6. Krishnan JA, Segal JB, Streiff MB, et al. Treatment of venous thromboembolism with low-molecular-weight heparin: a synthesis of the evidence published in systematic literature reviews. Respir Med. 2004;98:376-86.
7. Garcia DA, Baglin TP, Weitz JI, Samama MM. Parenteral anticoagulants: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest. 2012 ;141(Suppl 2):e24S-e43S.
8. Hull RD, Raskob GE, Brant RF, Pineo GF, Valentine KA. Relation between the time to achieve the lower limit of the APTT therapeutic range and recurrent venous thromboembolism during heparin treatment for deep vein thrombosis. Arch Intern Med. 1997;157:2562-8.
9. 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;119:874-81.
10. Cossette B, Pelletier ME, Carrier N, et al. Evaluation of bleeding risk in patients exposed to therapeutic unfractionated or low-molecular-weight heparin: a cohort study in the context of a quality improvement initiative. Ann Pharmacother. 2010 ;44:994-1002.
11. Bauer SR, Ou NN, Dreesman BJ, Armon JJ, Anderson JA, Cha SS, et al. Effect of body mass index on bleeding frequency and activated partial thromboplastin time in weight-based dosing of unfractionated heparin: a retrospective cohort study. Mayo Clin Proc. 2009;84:1073-8.
12. Thomas MP, Mahaffey KW, Chiswell K, et al. Activated partial thromboplastin time measurement is not associated with clinical outcomes in patients with high-risk non-ST-segment elevation acute coronary syndromes treated with unfractionated heparin. J Thromb Thrombolysis. 2012;34:114-9.
13. Hull RD, Pineo GF. Heparin and low-molecular-weight heparin therapy for venous thromboembolism: will unfractionated heparin survive? Semin Thromb Hemost. 2004 ;30(Suppl 1):11-23.
14. Smith SB, Geske JB, Maguire JM, Zane NA, Carter RE, Morgenthaler TI. Early anticoagulation is associated with reduced mortality for acute pulmonary embolism. Chest. 2010;137:1382-90.
15. Linke LC, Katthagen BD. Weight-based heparin dosing is more effective in the treatment of postoperative deep vein thrombosis. Arch Orthop Trauma Surg. 1999;119:208-11.
16. Lee HN, Cook DJ, Sarabia A, et al. Inadequacy of intravenous heparin therapy in the initial management of venous thromboembolism. J Gen Intern Med. 1995;10:342-5.
17. Guervil DJ, Rosenberg AF, Winterstein AG, Harris NS, Johns TE, Zumberg MS. Activated partial thromboplastin time versus antifactor Xa heparin assay in monitoring unfractionated heparin by continuous intravenous infusion. Ann Pharmacother. 2011;45:861-8.
18. Cheng S, Morrow DA, Sloan S, Antman EM, Sabatine MS. Predictors of initial nontherapeutic anticoagulation with unfractionated heparin in ST-segment elevation myocardial infarction. Circulation. 2009;119:1195-202.
19. Bernardi E, Piccioli A, Oliboni G, Zuin R, Girolami A, Prandoni P. Nomograms for the administration of unfractionated heparin in the initial treatment of acute thromboembolism--an overview. Thromb Haemost. 2000;84:22-6.

20. Rosborough TK, Shepherd MF. Achieving target antifactor Xa activity with a heparin protocol based on sex, age, height, and weight. Pharmacotherapy. 2004;24:713-9.

21. Dobesh PP. Unfractionated heparin dosing nomograms: road maps to where? Pharmacotherapy. 2004;24(8 Pt 2):142S-5S.

22. Holbrook A, Schulman S, Witt DM, Vandvik PO, Fish J, Kovacs MJ, et al. Evidence-based management of anticoagulant therapy: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest. 2012;141(2 Suppl):e152S-e184S.

23. Rosenberg AF, Zumberg M, Taylor L, LeClaire A, Harris N. The use of anti-Xa assay to monitor intravenous unfractionated heparin therapy. J Pharm Pract. 2010;23:210-6.

24. Manzato F, Mengoni A, Grilenzoni A, Lippi G. Evaluation of the activated partial thromboplastin time (APTT) sensitivity to heparin using five commercial reagents: implications for therapeutic monitoring. Clin Chem Lab Med. 1998;36:975-80.

25. Zehnder J, Price E, Jin J. Controversies in heparin monitoring. Am J Hematol 2012;87(Suppl 1):S137-S140.

26. Anand S, Ginsberg JS, Kearon C, Gent M, Hirsh J. The relation between the activated partial thromboplastin time response and recurrence in patients with venous thrombosis treated with continuous intravenous heparin. Arch Intern Med. 1996;156:1677-81.

27. Anand SS, Bates S, Ginsberg JS, et al. Recurrent venous thrombosis and heparin therapy: an evaluation of the importance of early activated partial thromboplastin times. Arch Intern Med. 1999;159:2029-32.

28. Smith SB, Geske JB, Maguire JM, Zane NA, Carter RE, Morgenthaler TI. Early anticoagulation is associated with reduced mortality for acute pulmonary embolism. Chest. 2010;137:1382-90.

29. Cuker A, Raby A, Moffat KA, Flynn G, Crowther MA. Interlaboratory variation in heparin monitoring: Lessons from the Quality Management Program of Ontario coagulation surveys. Thromb Haemost. 2010;104:837-44.

30. Raschke R, Hirsh J, Guidry JR. Suboptimal monitoring and dosing of unfractionated heparin in comparative studies with low-molecular-weight heparin. Ann Intern Med. 2003;138:720-3.

31. Eikelboom JW, Hirsh J. Monitoring unfractionated heparin with the aPTT: time for a fresh look. Thromb Haemost. 2006;96:547-52.