



Case Report

Anti Factor Xa Assay for Effective Monitoring of Heparin: A Case Report

Paluri R^{1*}, Darapu H², Koya S³, Marques S⁴

^{1&3}Hematology Oncology fellows, Department of Hematology Oncology, University of Alabama at Birmingham (UAB); Comprehensive Cancer Center, NP 2540, 1720 2nd Ave S, Birmingham, AL 35294,

²Internal Medicine Resident, Department of Internal Medicine, Baptist Health system, 3201 4th Ave S, Birmingham, AL, 35222,

⁴Professor of Medicine, Department of Laboratory Medicine, UAB, 1720 2nd Ave S, Birmingham, AL 35294.

ABSTRACT

Unfractionated Heparin (UFH) is a widely used anticoagulant for inpatient setting. This is routinely monitored by activated partial thromboplastin time (APTT) in several laboratories. However, this method has been associated with high degree of variability influenced by several factors. Very few cases of sub-therapeutic heparin in spite of appropriate APTT were reported. Here we describe a clinical case of deep venous thrombosis who was initially treated with heparin drip adjusted to therapeutic APTT, that eventually progressed to extensive thrombosis. Due to history of lupus, baseline elevation of APTT and possible sub-therapeutic dosage was suspected. Further investigation by checking anti-Xa levels revealed that patient had been sub therapeutically dosed with UFH, suggesting that APTT is not a reliable estimate for heparin monitoring.

KEYWORDS: Heparin monitoring; Lupus; anti factor Xa, APTT

INTRODUCTION

Heparin is a potent anticoagulant extensively used for prophylaxis and treatment of thromboembolic disorders. It is routinely monitored with the activated partial thromboplastin time (APTT). APTT has been used since 1972 and became standard of care to monitor heparin based on time and cost effectiveness [1]. Several patients were sub therapeutic when anti-factor Xa was compared with APTT for heparin levels in plasma[2]. The gold standard test to monitor heparin is the anti- factor Xa assay. It is a functional assay that facilitates the measurement of the direct inhibition of factor Xa by the heparin-anti-thrombin complex [3]. Since the APTT is a global measure of coagulation, a patient may appear to be receiving enough heparin because of a APTT in the therapeutic range and, yet, be sub-therapeutic when tested with the anti-Xa assay [4].

CASE REPORT

A 57-year-old female with common variable immunodeficiency and a Mediport in the left subclavian vein presented with abdominal pain and vomiting, was

diagnosed with acute pancreatitis. Her Mediport was found to be clotted and had to be removed. She was treated with heparin drip for four days and discharged on enoxaparin and warfarin for an overlap period of three days. Three weeks later, she presented with progressive neck pain and extensive thrombosis of the left subclavian internal jugular, brachiocephalic and axillary veins, extending into the sigmoid and superior sagittal sinuses and the jugular foramen of the skull was identified. A hypercoagulable evaluation revealed a history of estrogen replacement therapy for 30 years but no smoking or alcohol consumption.

There was also no family history of thrombosis. She was started on a heparin drip and an APTT a few hours later was 98s (heparin therapeutic range: 71-100s). However, the anti-Xa result was only 0.1 units/ml (therapeutic range for heparin: 0.3-0.7 units/ml) despite a normal antithrombin level. Laboratory evaluation for thrombophilia was positive for a lupus anticoagulant which prolonged the APTT. Thus, the APTT of 98s during heparin therapy was due to the combination of a lupus anticoagulant and effect of the drug.

Heparin infusion was increased until she achieved a therapeutic anti-Xa level. Her thrombosis resolved without any further intervention.

DISCUSSION

A baseline APTT prior to heparin initiation is essential to determine if a patient may be monitored with this assay. When the APTT is prolonged because of a lupus anticoagulant, such as in this patient, the anti-Xa assay must be employed. The anti-Xa assay is a chromogenic test that specifically determines the level of heparin in plasma [4]. It is superior to the APTT because it is not affected by pre-analytical variables such as specimen collection and processing and deficiencies or high concentrations of coagulation factors of the common and intrinsic pathways [5-7].

Although more expensive and complex than the APTT, the anti-Xa assay is also automated and may be cost-effective when considered that therapeutic anticoagulation may be ensured more readily. Some studies have reported that heparin therapeutic range could be achieved as early as seven to nine hours in patients monitored with the anti-Xa assay. It has cost advantage over APTT as it is associated with decreased requirement of heparin in those who are resistant to heparin, lesser changes in dosage and less nursing time[8]. In past few years, the assay became automated, cost effective and more accessible in many institutions. In addition to cases of prolonged baseline APTT, anti-Xa should be used when the patient is receiving a high dose of heparin and the APTT is not responding [9].

This phenomenon is often the result of high levels of factor VIII and fibrinogen, which shorten the APTT [10]. When using the anti-Xa to monitor intravenous heparin, the assay must be repeated six hours after every infusion adjustment in order to prevent under- and over anticoagulation [11]. The patients are potentially at high risk for bleeding unless the anti-Xa assay is used and the heparin dose adjusted according to patient related variables to keep it in the appropriate therapeutic range [12].

CONCLUSION

The limitations of exclusive APTT monitoring were well established. Plasma levels of heparin and antithrombotic effects of heparin are not being consistently correlated with APTT. However, several hospitals still continue to use APTT as it is easily available and cost effective. It is important to stress the value of using routine anti factor Xa assays for monitoring of UFH therapy for effective management, prevention of further dose-dependent thrombotic or hemorrhagic complications and also for safety of patient population. Therefore the antifactor-Xa assay with its superiority over APTT would certainly influence better patient outcomes.

REFERENCES

1. Valenstein PN, Walsh MK, Meier F. Heparin monitoring and patient safety: a College of American Pathologists Q-Probes study of 3431 patients at 140 institutions. *Arch Pathol Lab Med.* 2004 Apr;128(4):397-402
2. Vandiver JW, Vondracek TG. A comparative trial of anti-factor Xa levels versus the activated partial thromboplastin time for heparin monitoring. *Hosp Pract (1995) - Apr* 2013; 41(2); 16-24
3. Kitchen S. Problems in laboratory monitoring of heparin dosage. *Br J Haematol.* 2000 Nov;111(2):397-406.
4. Rabia T. A Review of Unfractionated Heparin and its Monitoring: St.John's University, Jamaica, New York. *US Pharm.* 2007;32(7):HS-26-HS-36.
5. Lehman CM, Frank EL. Laboratory monitoring of heparin therapy: partial thromboplastin time or anti-Xa assay? *Lab Medicine* 2009;40:47-51
6. Bates SM, Weitz JI. Coagulation assays. *Circulation* 2005; 12: e53-e60
7. Rosenberg AF, Zumberg M, Taylor L, LeClaire A, Harris N. The use of anti-Xa assay to monitor intravenous unfractionated heparin therapy. *Journal of Pharmacy Practice* 2010;23:210-6.
8. Rosborough TK. Monitoring unfractionated heparin therapy with antifactor Xa activity results in fewer monitoring tests and dosage changes than monitoring with the activated partial thromboplastin time. *Pharmacotherapy.* 1999 Jun;19(6):760-6.
9. Guervil DJ1, 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 Jul;45(7-8):861-8. doi: 10.1345/aph.1Q161
10. Paul N. Valenstein, MD; Molly K. Walsh, PhD; Frederick Meier, MD. Heparin Monitoring and Patient Safety A College of American Pathologists Q-Probes Study of 3431 Patients at 140 Institutions. *Arch Pathol Lab Med.* 2004;128:397-402
11. Armando Tripodi, Veena Chantarangkul, Ida Martinelli, Paolo Bucciarelli, and Pier Mannuccio Mannucci. A shortened activated partial thromboplastin time is associated with the risk of venous thromboembolism. *Blood,* 2004; 104-12
12. Smith ML, Wheeler KE. Weight-based heparin protocol using antifactor Xa monitoring. *Am J Health-Syst Pharm* 2010; 167:371-4

*Corresponding author: Dr Ravi Kumar Paluri
E-Mail: rpaluri@uabmc.edu