



Case Report

Utilization of thromboelastography and a low molecular weight heparin anti-Xa assay for guidance in apixaban reversal: A case report



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ABSTRACT

Reversal of oral factor Xa (FXa) inhibitors, such as apixaban, remains a controversial topic. However, the controversy goes beyond what reversal agent to utilize. Often times these patients present with an acute major bleed and are difficult to assess whether reversal is warranted or not. Furthermore, it is difficult to assess whether reversal was successful in a timely manner. A paucity of literature exists regarding the utilization of low molecular weight heparin (LMWH) anti-Xa assays and thromboelastography for identifying coagulopathies associated with oral FXa inhibitors. We report a case of apixaban induced coagulopathy utilizing thromboelastography and a LMWH anti-Xa assay as a guide for reversal.

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1. Background

Reversal of oral factor Xa (FXa) inhibitors, such as apixaban, remains a controversial topic. There is an indistinct direction on identifying those that need reversal, which agent to utilize, and how to measure successful reversal [1]. While specific anti-Xa assays exist for apixaban, rivaroxaban, and edoxaban they are expensive and not readily available at most institutions. There is data available evaluating the utility of low molecular weight heparin (LMWH) anti-Xa assays for identifying FXa inhibitor activity; however, it is not robust and has not been validated in a randomized fashion [2]. Alternatively, rapid thromboelastography (r-TEG) has been evaluated in healthy volunteers and could serve a role in identifying patients that need reversal without erroneous factor or blood product administration [3]. We report a case of an acute major bleed associated with the presence of apixaban, assessed with both r-TEG and a LMWH anti-Xa assay to help guide the need and success of reversal utilizing four factor prothrombin complex concentrate (PCC).

2. Case

A 92 year old male presented to the emergency department after a fall from standing position striking his head with a developing scalp hematoma and with initial complaint of headache. The patient was noted

to be on apixaban for a history of atrial fibrillation, of which the time of last known ingestion was unknown. He was bradycardic with a heart rate in the 50's and hypertensive with a systolic blood pressure in the 200's. A non-contrast computed tomography (CT) of the head revealed a subdural hematoma of approximately 1.1 cm. Given the clinical presentation, image findings, and unknown time of last ingestion of apixaban, a LMWH anti-Xa assay and r-TEG were obtained to identify whether the patient warranted reversal. The LMWH anti-Xa assay was reported at 1.83 units/mL and the initial r-TEG (Fig. 1) had a prolonged ACT time (136 s). Given the image findings and prolonged anti-coagulation results the decision was made to reverse the anticoagulation effect of apixaban with PCC (25 units/kg; 100 kg). After reversal, a repeat r-TEG (Fig. 2) and LMWH anti-Xa assay were performed to assess the need for additional PCC doses. There was reduction in R and ACT times noted compared to the initial r-TEG and there was a reduction in LMWH anti-Xa activity to 1.36 units/mL. Table 1 shows the initial and post reversal anticoagulation parameters measured. A repeat head CT 2 h after PCC reversal showed no increase in hematoma volume and no subsequent doses of PCC were given.

3. Discussion

First, while lack of routine laboratory monitoring is a benefit for the FXa inhibitors in the ambulatory care setting, it can prove problematic in acute care situations. Given the increasing utilization of these agents, it is imperative in acute major bleeds to identify coagulopathy early.

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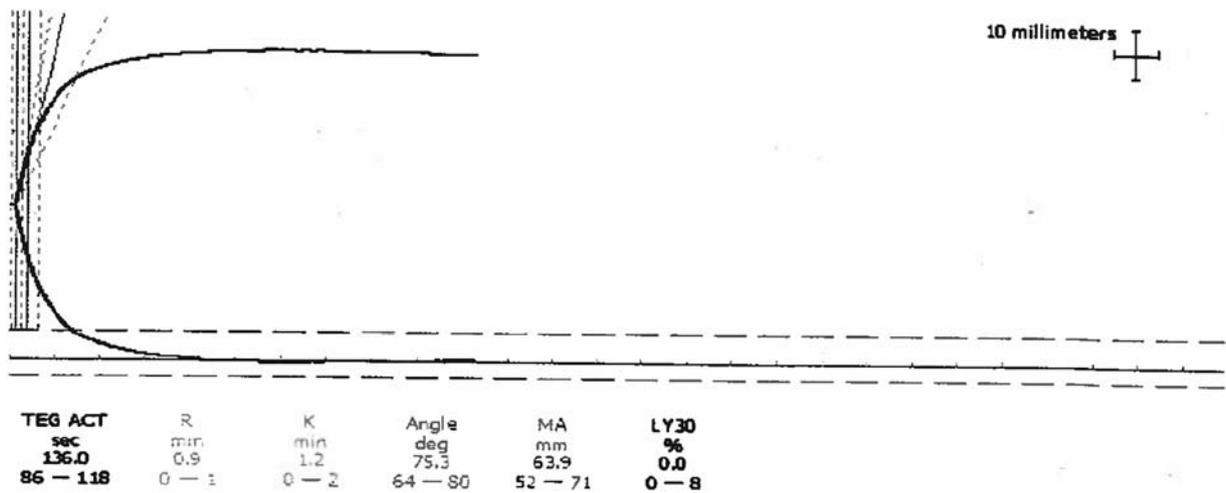


Fig. 1. Initial rapid-thromboelastography values.

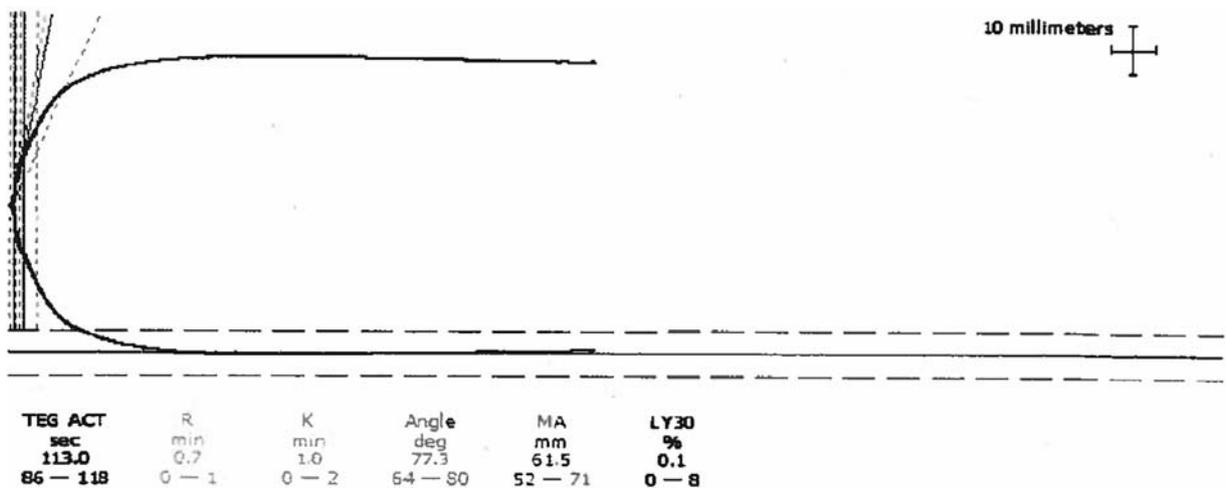


Fig. 2. Post prothrombin complex concentrate rapid-thromboelastography values.

There is a paucity of data on the ideal laboratory test for these agents. Based on previously reported data, we proposed the utilization of both r-TEG and LMWH to mitigate erroneous reversal. Additionally, given that agents such as, andexanet alfa, have the potential to place a significant financial burden on many institutions, utilizing available laboratory tools may be imperative for optimal guidance of reversal [4].

Second, it will be important to assess the clinical meaning of reversal of these laboratory tests. Just as reversal of INR with warfarin associated bleeds is a surrogate marker for hemostasis, we must also correlate r-TEG and LMWH anti-Xa assay correction as it relates to hemostasis in FXa inhibitor associated bleeds. While no set values have been validated for identifying FXa associated bleeds with LMWH anti-Xa assays, a proposed cut off of <0.5 units/mL may indicate negligible FXa inhibitor serum concentrations [2]. In our case, we had reduction in anti-Xa

activity by 0.47 units/mL but were still above the threshold of 0.5 units/mL. However, given the reduction in ACT values from the r-TEG, the decision was made to defer additional reversal and the follow up head CT confirmed our decision was appropriate. One of the largest trials evaluating oral FXa inhibitor reversal, the ANNEXA-4 trial, found that reduction in anti-Xa activity did not predict achievement of good or excellent hemostasis [5]. It is important to note that this trial was a single non-blinded study without a comparator group and must be interpreted with caution. Interestingly, while the follow up r-TEG after reversal was normal the anti-Xa level remained elevated, which did not have an obvious explanation.

Lastly, r-TEG may be beneficial at assessing other coagulopathies expressed in addition to FXa inhibitor associated bleeding. Patients commonly take concomitant anti-platelets in addition to FXa inhibitors.

Table 1
Initial and post reversal coagulation parameters.

Parameter	Prior to reversal	Post reversal	Reference range
Citrated R time (minutes)	0.9	0.7	0.3–0.8
Citrated K time (minutes)	1.2	1.0	0.5–2.3
Citrated alpha angle (degrees)	75	77	64–80
Citrated maximum amplitude (mm)	64	62	52–71
Activated clotting time (seconds)	136	113	86–118
Low molecular weight heparin anti-Xa assay (units/mL)	1.83	1.36	Prophylaxis: 0.2–0.5 Treatment: 0.6–2.0

Ultimately, the presence of anti-platelet effects cannot be assessed by anti-Xa assays but possibly identified via r-TEG and help guide early resuscitation [6]. Currently, there is limited evidence on resuscitation of oral FXa inhibitor or anti-platelet associated bleeds, but r-TEG could serve a vital role in the future. Here we report a case of r-TEG and LMWH anti-Xa assay utilization for reversal of apixaban associated acute major bleed.

Declaration of Competing Interest

None.

References

- [1] Gilbert BW, Reeder JA, Alkhalifah MA, et al. Throwing it in reverse: an update on reversal of oral factor Xa inhibitors. *Am J Emerg Med* Apr 8 2019. <https://doi.org/10.1016/j.ajem.2019.04.007> pii: S0735-6757(19)30227-X. [Epub ahead of print].
- [2] Billoir P, Barbay V, Joly LM, et al. Anti-Xa oral anticoagulant plasma concentration assay in real life: rivaroxaban and apixaban quantification in emergency with LMWH calibrator. *Ann Pharmacother* Apr 2019;53(4):341–7.
- [3] Dias JD, Lopez-Espina CG, Ippolito J, et al. Rapid point-of-care detection and classification of direct-acting oral anticoagulants (DOACs) with the TEG® 6s: implications for trauma and acute care surgery. *J Trauma Acute Care Surg* Apr 29 2019. <https://doi.org/10.1097/TA.0000000000002357> [Epub ahead of print].
- [4] Gilbert BW, Reeder JA. Comment: andexanet alfa: a novel factor Xa inhibitor reversal agent. *Ann Pharmacother* May 29 2019;1060028019855160. <https://doi.org/10.1177/1060028019855160> [Epub ahead of print].
- [5] Connolly SJ, Crowther M, Eikelboom JW, et al. Full study report of andexanet alfa for bleeding associated with factor Xa inhibitors. *N Engl J Med* Apr 4 2019;380(14):1326–35.
- [6] Wu Z, Liu AF, Zhou J, et al. The safety of triple antiplatelet therapy under thromboelastography guidance in patients undergoing stenting for ischemic cerebrovascular disease. *J Neurointerv Surg* Apr 2019;11(4):352–6.