ASSESSING ANTICOAGULATION SAFETY AND EFFICACY IN ANTIPHOSPHOLIPID SYNDROME PATIENTS MONITORED BY FACTOR II ACTIVITY ASSAY

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ABSTRACT

Objective: To determine if monitoring antiphospholipid syndrome (APS) patients on warfarin by factor II activity assay (FIIAA) would decrease thrombus risk or if elevating international normalized ratio (INR) goal based on FIIAA would increase bleeding risk.

Methods: A community hospital retrospective chart review was conducted on anticoagulation clinic APS patients (n=49) over 50 months. Patients with an APS-associated diagnosis compliant warfarin therapy were included as long as they were at least 18 years of age. Patients were excluded if they were monitored in the clinic for <6 months, became pregnant, or developed cancer during the study period. The primary outcome was to determine if FIIAA monitoring reduced thrombus risk or increased bleeding risk.

Results: No statistical difference in bleeding event, age, comorbidities, or sex was determined between the FIIAA monitored and non-FIIAA monitored group. Thromboembolic events approached statistical significance (p=0.053) in the monitored group. Two of the 3 patients had a subtherapeutic INR and one had additional thrombophilias.

Conclusion: Thromboembolic risk was not reduced by FIIAA monitoring in APS patients. INR goal increases based on FIIAA monitoring did not increase bleeding risk. A larger study may help determine the most appropriate way to monitor APS patients using warfarin.

Keywords: Antiphospholipid syndrome, Factor II activity assay, Warfarin, Thrombosis, Anticoagulation and bleeding.

INTRODUCTION

Monitoring and management of anticoagulation in antiphospholipid patients are challenging, and the most appropriate method of anticoagulation monitoring is controversial [1]. The objective of this study is to determine if monitoring antiphospholipid syndrome (APS) patients on warfarin by factor II activity assay (FIIAA) would decrease thrombus risk or if elevating international normalized ratio (INR) goal based on FIIAA would increase bleeding risk.

APS is a prothrombotic condition characterized by the presence of autoantibodies that target phospholipid-bound proteins [1]. Although these antibodies are known to be present in this patient population, it is still not completely understood why these antibodies place patients in a hypercoagulable state [1]. The development of APS is very rare among the general population with 1-5% incidence in young healthy adults. This syndrome is more often associated in patients who have been diagnosed with systemic lupus erythematosus, anywhere from 12% to 34% of lupus patients would test positive for APS. The typical age of onset is around 30-40 years of age and rarely diagnosed after the age of 60 [2].

It is widely accepted that these patients should be on anticoagulation therapy, but what is still debated is how to appropriately monitor these patients. The antibodies associated with APS prolong prothrombin times. The Coaguchek® INR meter package insert has the following limitation of procedure: "The presence of anti-phospholipid antibodies (APAs) such as lupus antibodies can potentially lead to prolonged clotting times, i.e., elevated INR values. A comparison to an APA-insensitive laboratory method is recommended if the presence of APAs is known or suspected [3]."

According to the 2012 and 2015 CHEST guidelines, it is recommended for patients with APS and previous thromboembolism to be placed on vitamin K antagonist therapy with an INR goal range of 2.0-3.0 [4]. However, several studies have shown that patients with APS have a prolonged prothrombin time due to the antibodies that are present in this disease state. The antiphospholipid condition can interfere with thromboplastins used in traditional point of care (POC) and venous INR monitoring [5-9].

The previous studies have evaluated the correlations of prothrombin to INR, FIIAA, and chromogenic factor X (CFX) testing. All studies proved that many patients had prolonged prothrombin time, which was leading to falsely elevated INR levels in this patient population [5-8,10]. The data suggest that alternative monitoring methods such as FIIAA and CFX are unaffected by the antibodies that APS patients develop. Having more accurate anticoagulation monitoring utilizing the FIIAA laboratory test should help prevent recurrent thromboembolism in APS patients that may not be protected at the typical INR goal range of 2-3. However, the debate still exists whether FIIAA or CFX is the most reliable method to monitor this patient population. To the author's knowledge, there are no studies comparing the safety and effectiveness of monitoring as well as adjusting therapeutic goals of warfarin therapy in APS patients utilizing the phospholipid-independent FIIAA laboratory test.

METHODS

Study design

The study was a retrospective chart review conducted on APS patients on warfarin therapy seen at all five health system anticoagulation clinics. Electronic medical records were reviewed for the diagnosis codes of antiphospholipid antibody, anticardiolipin antibody, or lupus anticoagulant seen at any of the anticoagulation clinics during the study period of April 2010 through July 2015. FIIAA was chosen as the phospholipid-independent anticoagulation monitoring test due

to the similar monitoring effectiveness and decreased cost compared to CFX [4]. The goal or therapeutic FIIAA range was elected to be 15-25% based on the previous literature recommendations [5-6]. The comparative study groups were divided into FIIAA monitored and non-FIIAA monitored patients. Patients in the monitored group had FIIAA monitored throughout their clinic visits along with POC and venous INRs. INR goal ranges were adjusted according to the policy in place (Fig. 1). Non-FIIAA monitored group patients were evaluated solely by POC INR. Warfarin dose adjustments were based on venous INR measurements in the FIIAA monitored group and POC INR in the non-FIIAA monitored patients. Adjustments in INR goal ranges were based on the FIIAA percentage in the monitored group.

The primary outcome was to evaluate if monitoring FIIAA in APS patients would reduce the risk of thrombosis development without increasing the risk of a bleeding event.

Thromboembolic events were defined as any clinical evidence of a thrombus. Bleeding events were divided into two categories, major, or minor based on criteria set by the International Society on Thrombosis and Hemostasis [11]. Major bleeding events were defined as: Any event that caused fatality, symptomatic bleeding in a critical area or organ, hemoglobin decrease by >2 g/dL, or transfusion requiring >2 units of whole blood or red blood cells. Minor bleeding included any patient-reported bleeding and confirmed diagnosis in medical record that did not require any additional tests, referrals, or medical visits.

Secondary outcomes included the percentage of patients prescribed an INR goal range above 2.0-3.0, percentage of each study group with a confirmatory second thrombophilia test at least 12 weeks or more from the initial positive thrombophilia test to confirm the APS diagnosis, as well as the percentage of patients below and above range during the study period.

Inclusion and exclusion criteria

Patients from any health network anticoagulation clinic were included if they were >18 years of age and had one of the following diagnoses codes: Antiphospholipid antibody (or syndrome), anticardiolipin antibody, or lupus anticoagulant. Patients were excluded if they had not been followed in the clinic for at least 6 months if they became pregnant or were diagnosed with cancer during the review period. Bleeding and thromboembolic events were also excluded if they occurred within 6 weeks of surgery, as they were deemed provoked events. Five patients were excluded in the FIIAA monitored group and seven patients in the non-FIIAA monitored group. After evaluation of inclusion and exclusion criteria, the comparative study groups included 19 patients in the FIIAA monitored and 30 patients in the non-FIIAA monitored group.

Data collection and analysis

Data points collected include: Demographics, diagnosis code, if a second confirmatory diagnosis thrombophilia test was completed at least 12 weeks after the first positive thrombophilia test, INR goal ranges, FIIAA levels, percentage of INR values above and below goal range, comorbidity scores, any thrombosis or bleeding events, and INR (POC and/or venous) at the time of thrombosis or bleeding events. The Charlson Comorbidity Scores were assessed with a point system based on chart diagnosis of the following: Cardiac (previous myocardial infarction, stroke, peripheral vascular disease or congestive heart failure), peptic ulcer disease, liver disease, renal disease, diabetes, pulmonary disease, hemiplegia, cancer, AIDS, and/or rheumatic disease [12].

Statistical analysis

The Minitab® statistical software was utilized to analyze data through Northern Kentucky University Burkhardt Consulting Center. A Fischer's exact test was performed for the primary outcomes between the two study groups and to detect any difference in male to female ratio in each study group. An independent t-test was performed for the differences in percent of INRs above or below range as well as age between the two study groups. Two-sample t-test was also conducted to determine comorbidity score differences among each study group.

RESULTS

After the electronic medical records were reviewed there were a total of 61 patients that met inclusion criteria (Fig. 2). Of the 61 patients, 24 were categorized into the FIIAA monitored group before exclusion criteria application. Of the 24 patients, 5 were excluded leaving 19 FIIAA monitored study patients: Two for confirmatory testing at 12 weeks that was negative, 2 for follow up for <6 months, and 1 with a diagnosis of cancer. 37 patients were categorized into the non-FIIAA monitored group before exclusion criteria application. Seven patients were excluded leaving 30 non-FIIAA monitored patients: Six for follow-up <6 months and 1 was a self-diagnosed patient. There were no statistically different baseline characteristics among the two groups (Table 1).

Primary outcomes

Three thromboembolic events occurred in the FIIAA monitored group, and no thromboembolic events occurred in the non-FIIAA monitored group. No statistically significant reduction occurred in thrombosis risk between the FIIAA monitored and non-FIIAA monitored patients (p=0.053). Two of the three patients had a subtherapeutic INR at the time of the thromboembolic event. One of the thromboembolic event patients had additional thrombophilias (protein C deficiency and methylenetetrahydrofolate reductase heterozygous mutation) which would have placed them at higher risk for a thromboembolism
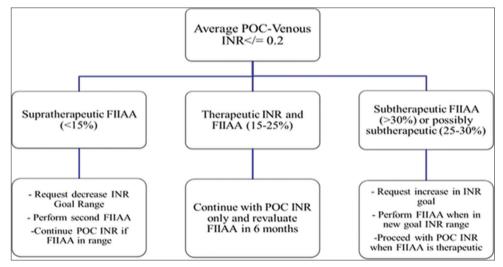

Fig. 1: Monitoring policy. POC: Point of care, INR: International normalized ratio

compared to patients who had the singular risk factor for recurrent thromboembolism due to APS. On admission for the thromboembolism, the multiple thrombophilia patient's INR was 2.99 (goal 2.8-3.5), and the patient was considered to have a warfarin failure. This patient had a recurrent thromboembolism after being non-compliant with INR monitoring for 4 months. A second patient had limited movement of his knee secondary to a knee injury and held his warfarin for 4 days without medical advice. He subsequently developed an ultra-sound confirmed deep vein thrombosis on the 3rd day of self-holding warfarin resulting in an INR of 1.3 (goal 2.5-3.5). A third patient had a pulmonary embolism with a subtherapeutic INR of 2.1 (goal 3-4) shortly after a fall.

There was one bleeding event in the non-FIIAA monitored group and no bleeding events in the FIIAA monitored patient group, reaching no statistically significant difference among the two patient groups (p=1.0). One patient in the non-FIIAA monitored group had an episode of hematuria with an INR of 3.6. The patient was diagnosed with kidney stones during the admission.

Secondary outcomes

A total of 74% of the FIIAA monitored group had a prescribed INR goal range above 2.0-3.0 compared to only 16% of the non-FIIAA monitored group. In the patients monitored by FIIAA, approximately, 29.16% of INRs were below goal range, while 20.4% were above goal range. The results were similar in the patients not monitored by FIIAA with 33.94% of INRs above goal range and 17.74% of INRs below goal range.
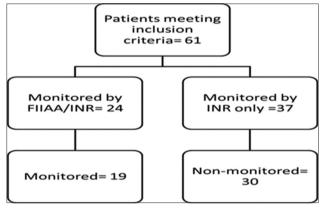

Fig. 2: Data collection

No statistical difference (p=0.347, p=0.315) was detected in the percent of INRs above or below goal INR range between study groups (Table 2).

Approximately, 20% of patients in each study group had a confirmatory second thrombophilia test at least 12 weeks or more from the initial positive thrombophilia test to confirm the APS diagnosis. The APS/unknown category was patients with a confirmed APS diagnosis by a hematologist or physician from an outside health-care facility without laboratory records being able to be confirmed.

DISCUSSION

The best method of anticoagulation monitoring in APS patients is a debated topic in the medical literature. INR monitoring instruments traditionally used to monitor clotting times in anticoagulated patients have limitations of procedure stating patients with APS should have a phospholipid-independent measure of anticoagulation [3]. Many anticoagulated APS patients are managed by INR monitoring alone. The goal of this study is to detect a difference in effective and safe monitoring of anticoagulation in APS patients using the FIIAA phospholipid-independent test. It is well known that APS patients may have a falsely-elevated venous or POC INR [4,5]. For example, a patient in the FIIAA monitored study group had an elevated baseline INR of 1.8 without prior use of an oral anticoagulant.

About three-quarters of the FIIAA monitored had an INR goal range above the typical 2-3 range. This was to be expected in the FIIAA monitored patients, as INR goal ranges were adjusted according to subtherapeutic FIIAA results. The patients in the non-FIIAA monitored group had INR goal ranges set by the physician with no recommendations for INR goal increases.

The thromboembolic event rate approached statistical significance (p=0.053) with 3 patients having a thromboembolic event in the FIIAA monitored group. One of the patients presenting with a subtherapeutic INR had limited mobility and self-held warfarin doses without medical advice. This thromboembolic occurrence would be considered a provoked event. With two patients presenting with INR below goal range due to dosing or INR monitoring non-compliance, it could be argued that only one patient developed a thromboembolism while being properly anticoagulated. In addition, one of the thromboembolic events was a pulmonary embolism when the patients INR was 2.1 (goal 3-4) after being non-compliant with INR monitoring for several months. This particular study patient, though non-compliant demonstrates the value

Table 1: Baseline characteristics

Characteristics	FIIAA monitored	Non-FIIAA monitored (N=30)	p value
Sex			0.327
Male	9	10	
Female	10	20	
Age	55.9±16.5	51.2±11.0	0.273
Comorbidity score	2.47±2.74	2.93±1.96	0.530
Confirmatory test at least 12 weeks after initial test	21%	23%	
Diagnosis			
LA	6	13	
aCL	3	2	
LA and aCL	1	4	
APS/unknown	6	11	

FIIAA monitored group sample size=19, Non-FIIAA monitored group sample size=30. Values are expressed as mean±SD. Not significant at **p<0.05 as compared to each group using a two-sample t-test. LA: Lupus anticoagulant, aCL: Anti-cardiolipin antibodies, SD: Standard deviation, APS: Antiphospholipid syndrome, FIIAA: Factor II activity assay

Table 2: INRs in range

Secondary outcomes	FIIAA monitored group	Non-FIIAA monitored group
% INRs below goal range (p=0.347)	29.16%	33.94%
% INRs above goal range (p=0.315)	20.4%	17.74%

INR: International normalized ratio, FIIAA: Factor II activity assay

of utilizing the FIIAA to truly target the appropriate INR goal range for APS patients. Anticoagulation monitoring of this study APS patient by INR alone would not have detected a need to increase the INR goal range above the standard 2-3 INR goal range. If this particular patient had not had their INR goal range increased from 2-3 up to 3-4, they likely would have had a recurrent thromboembolism within a presumed effective goal if his INR range had remained at the standard 2-3 range.

No statistical difference in bleeding was found between the FIIAA monitored or non-FIIAA monitored group. No association for bleeding risk was detected for patients with INR goal increases based on subtherapeutic FIIAA, but the small sample size may have limited the ability to detect a difference in regard to safety and effectiveness.

Only a fifth of the patients in each study group had a confirmatory second thrombophilia test at least 12 weeks or more from the initial thrombophilia test to confirm the APS diagnosis. False positive tests may occur during the acute thromboembolism period and thus a second, later test is recommended [7]. The lack of a confirmatory second thrombophilia test communicates a need to educate practitioners regarding the recommendation for a second thrombophilia test at least 12 weeks or more from the first positive thrombophilia test to confirm the diagnosis of APS. This study also indicates the lack of anticoagulation monitoring practitioners contacting prescribers to order a second thrombophilia test to confirm an APS diagnosis.

The previous studies of FIIAA and CFX anticoagulation monitoring have shown these tests are unaffected by the antibodies that APS patients develop. To the author's knowledge, there are no studies to compare how monitoring and adjusting warfarin therapeutic goals by FIIAA affect thromboembolic or bleeding events. This study does confirm previous literature regarding the lack of correlation of INR in APS patients as evidenced by the amount of FIIAA-monitored patients who had an INR goal range adjustment based on FIIAA results. The importance of this current study demonstrates the need for larger patient numbers and additional studies to detect the effect of the FIIAA monitoring on prevention of thromboembolism and effect on bleeding risk.

Limitations

Several known limitations existed throughout this study. The single-center design and small sample size (n=49) limited the ability to detect true thrombosis and bleeding risk between monitoring study groups in this patient population. The chance of a thromboembolic or bleeding event occurring at another area hospital is also a possible limitation due to reliance of patient self-reporting, which could have led to underreporting of both thrombosis and bleeding events. In addition, >75% of the patients did not meet diagnosis criteria for APS, as confirmatory testing at 12 weeks or greater was not completed or completed at an unknown outside facility. This lack of confirmatory testing limits the applicability to the general APS population. The retrospective chart review design also limits the amount of information that was able to be collected. If data points were missing in the patient chart, there was no method to collect the missing information.

CONCLUSIONS

The 2012 and 2015 CHEST guidelines recommend APS patients have a goal INR range of 2.0-3.0. Several studies have proven that prothrombin time is often prolonged in these patients which lead to a lack of protection from venous thromboembolism in patients with this more severe thrombophilia. FIIAA, which is unaffected by the antibodies that are characteristic in APS, is an alternative monitoring option for these patients. This study did not detect a significant reduction in thrombosis risk in APS patients whose goal INR ranges were adjusted according to FIIAA results, which was likely limited by the small patient population and single-center design. Although thrombosis risk was not reduced, bleeding events

were not more likely in the patients with increased INR goal ranges secondary to adjustment after subtherapeutic FIIAA. More efficacious anticoagulation by customizing an APS patient's INR goal range with FIIAA monitoring may prevent recurrent thromboembolism and needs to be further studied in larger, multicentered trials. The prevention of recurrent thromboembolism by identifying an APS-customized INR range, could potentially reduce morbidity and mortality in APS patients, but needs further study.

The current study also demonstrates a need for educating practitioners to order a second confirmatory thrombophilia test at least 12 weeks apart from the initial positive thrombophilia test.

This study was likely underpowered to detect the safety and effectiveness difference between monitoring anticoagulation with or without FIIAA in the APS patient. In the future, additional studies with a larger amount of patients in multicenter trials will need to be conducted to determine the true risk of thrombosis in these patients and how to effectively monitor anticoagulation status despite the antibodies that are developed in this disease state.

The authors have no actual or potential conflict of interest in relation to this original research article.

The author declares that written informed consent was obtained from the patients for release of medical information for education and research purposes. The patients were not identified in this case report according to standard hospital HIPPA policies.

The Ethical approval was given by the Institutional Review Board of the Health System and followed throughout the study period.

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