

Current practices for lupus anticoagulant testing at a tertiary care hospital and impact on laboratory resources

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BACKGROUND AND OBJECTIVES: The lupus anticoagulant (LA) test is an advanced test that is time consuming and requires a highly trained lab specialist. A high proportion of clinicians do not adhere to international guidelines and request the test inappropriately.

DESIGN AND SETTINGS: This descriptive study covered the period from January 2012 and January 2013 at the Hematology Laboratory at King Khalid University Hospital, Riyadh.

PATIENTS AND METHODS: The 274 lupus anticoagulant requests were categorized as proper or improper based on the guidelines of the International Society of Thrombosis and Haemostasis (ISTH). Data on numbers of requests and cost are summarized.

RESULTS: Of the 274 requests, 222 (81%) were classified as proper while 52 (19%) requests did not satisfy ISTH guidelines. The most frequently encountered incorrect indications were warfarin therapy (46%), heparin therapy (27%), a normal aPTT with no clinical indication (25%) and low serum fibrinogen levels (2%). The total cost of all improper requests was about 41 080 SAR (10 954 USD).

CONCLUSION: A majority of improper requests were related to anticoagulant therapy, which highlights the importance of implementing a comprehensive diagnostic algorithm for patients on warfarin and heparin therapy.

Lupus anticoagulants (LA) are a group of heterogeneous autoantibodies specific for phospholipids and binding proteins associated with the cell membrane. In vitro, LA prolongs activated partial thromboplastin time (aPTT), mimicking a factor deficiency.¹ However, in vivo LA is associated with a risk of thrombosis rather than bleeding so the name of the antibody is actually a misnomer. LA is implicated in several clinical conditions necessitating its proper standardization to avoid false positive and false negative results.^{2,3}

A number of factors can influence the performance of this test. Antibody heterogeneity, reagent variations and differences in analytical platforms have been implicated in inter- and intra-laboratory discrepancies.⁴⁻⁶ The publication of several consensus guidelines in recent decades has improved the specificity and sensitivity of the LA test.⁷⁻¹⁰ An update of the International Society on Thrombosis and Hemostasis (ISTH) guidelines pub-

lished in late 2009 became the cornerstone of routine laboratory practice and research.⁷ These guidelines have contributed significantly in the improved quality and reliability of LA testing.

The recommendations of the ISTH guidelines focus particularly on the need for correct patient selection to minimize inappropriate requisition for LA. According to the ISTH guidelines, LA testing should be limited to patients with higher clinical index of suspicion for having the antiphospholipid syndrome (APS) or who have prolonged aPTT without an apparent cause. The guidelines discourage requisition of the LA test for asymptomatic patients to avoid the risk of obtaining false-positive results that are frequently encountered due to the poor specificity of the assay. The false-positive results are of particular concern because they qualify patients for long and unnecessary oral anticoagulant treatment. Moreover, LA testing among patients receiving warfarin and a therapeutic dose of unfractionated

heparin should be postponed for a suitable time after discontinuation of anticoagulation as it may yield an erroneous result. For unfractionated heparin, both the hexagonal phospholipid assay and the dilute Russell viper venom time contain heparin neutralizers. However, the neutralizers are effective only up to specified levels (0.8-1.0 U/mL) that usually cover prophylactic doses of low molecular weight heparin (LMWH), but not the therapeutic doses of unfractionated heparin.¹¹⁻¹³ Vitamin K antagonists (VKA) prolong the basal clotting time and thus compromise the quality of lupus anticoagulant testing; therefore, testing of such samples is not recommended, especially if the international normalized ratio (INR) is more than 1.5.^{7,14} The best approach to patients on long-term VKA is to bridge to LMWH for 2 weeks following VKA discontinuation and to draw a blood sample after 12 hours from the last LMWH dose. Dilution of patient plasma with pooled normal plasma dilutes the LA titer and could lead to an underestimation of the weak LA inhibitor.⁷

This study was performed to assess the initial requisitions for the LA test by clinicians to determine whether the LA test was being requested in accordance with ISTH guidelines. In the event of discrepancies, we evaluated the burden on laboratory resources at King Khalid University Hospital, Riyadh.

PATIENTS AND METHODS

This study was conducted at the Hematology Laboratory at King Khalid University Hospital, Riyadh from January 2012 to January 2013. Requests for LA tests were categorized as proper or improper based on compliance with guidelines of ISTH. The criteria for proper LA test requests include an unexplained prolonged aPTT with normal fibrinogen in patients not receiving either heparin or warfarin therapy. LA test requisitions for patients with clinical evidence of thrombosis or fetal loss with normal aPTT were also included in this group.

The criteria for improper requests were requests for patients receiving unfractionated heparin or warfarin therapy (INR <1.5), low serum fibrinogen levels, a normal aPTT and an absence of clinical indications. For all the requests, it is mandatory to perform aPTT, throm-

boplastin time (TT) and fibrinogen levels prior to testing for LA. The international normalized ratio (INR) was performed only for patients receiving treatment with warfarin. For all requests with normal aPTT, the patients' files were reviewed carefully for the presence or absence of other indications such as a thrombotic event or fetal loss.

RESULTS

During the 12-month study period, of 274 lupus anticoagulant requests, 222 (81%) were proper and fulfilled the ISTH criteria. Most tests were ordered for females and the median age was 45 years (Table 1). For the 52 (19%) LA requests that did not satisfy ISTH requisition indications (Figure 1), the most common reasons were warfarin therapy for 24 requests (46%), heparin therapy for 14 (27%), a normal aPTT with no clinical indication for 12 (25%), and LA requisitions for patients with normal aPTT with no clinical indication and only one (2%) request for a patient with low serum fibrinogen levels (Figure 1). The cost of each test was estimated as 790 SAR (210 USD). The cost of all improper requests was about 41 080 SAR (10 954 USD) (Table 2).

DISCUSSION

We found that 19% of lupus anticoagulant requests in the hematology laboratory at KKHU were improper, indicating that approximately one-fifth of clinicians did not adhere to internationally recommended guidelines for LA testing.⁷ Several factors have been implicated in the increasing numbers of improper requests for such tests. These include lack of proper compliance with the recommended guidelines, inappropriate requisition partly due to inadequate knowledge, requisition of advanced tests from different departments by different physicians, including residents, registrars and consultants, inadequate request forms and lack of communication.^{15,16} The effect of rigorous adherence to the recommended guidelines on improvement in testing quality was evaluated by British group after dissemination of national guidelines on laboratory methods. The study revealed a compliance rate of 97% to the national guidelines, which was associated with significant improvement in efficacy and proper use of the LA test.¹⁷ Moreover, it also indicated a higher degree of consensus between clinicians and laboratory services. In the present study, however, we found relatively low compliance (81%) to the internationally recommended guidelines. In addition, issues related to inadequacy of requisition forms have been effectively rectified by introduction of electronic requisition forms.¹⁸ Electronic forms require

Table 1. Requests for lupus anticoagulant testing.

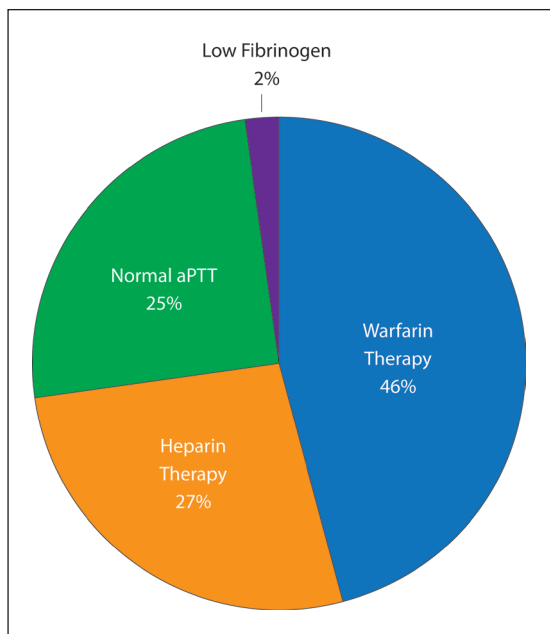
Type of request	Number	Female	Male	Median age
All requests	274	159 (58.03%)	115 (41.97%)	46 years
Proper requests	222 (81%)	131 (59%)	91 (41%)	45 years
Improper requests	52 (19%)	28 (53.85%)	24 (46.15%)	48.5 years

Table 2. Costs of lupus anticoagulant test.

Test	aPTT with mixing study	Thrombin time	PTT-LA and Staclot-LA	DRVVT-s and DRVVT-C	Staff fare	Total cost per request
Price (Saudi Riyal)	60	35	230	390	75	790
Price (USD)	16	9	61	104	20	210

the requesting physicians to furnish relevant information on clinical history, physical examination and particular details on drug and dietary history.

We also found that a majority of clinicians were tempted to request an LA test while their patients were being treated with either warfarin or heparin. The validity of LA testing in patients being treated with anticoagulants is questionable, firstly due to the long half life of warfarin, which extends over two weeks, and secondly due to the high incidence of false-positive results that may predispose patients to prolonged and avoidable oral anticoagulant therapy.^{7,11,19} In the present study, 46% of patients were investigated for LA. Although the rationale for the request was often difficult to ascertain, either lack of awareness among the requesting physicians or possibly challenges associated with discontinuation of warfarin therapy for diagnostic purposes on part of the treating physician, might be explanations.⁵⁻⁷ In contrast to these observations, the percentage of requests made without clinical indications and a normal aPTT indicates inadequate knowledge on the part of requesting physicians, which contributes to surging numbers of improper requests. Random screening for lupus anticoagulant is highly discouraged owing to the poor specificity of the available LA assays, which may lead to serious consequences in some patients due to the bleeding risk of anticoagulant therapy.^{7,11} Moreover, it adds to the huge burden on laboratory services. Laboratory testing for lupus anticoagulant is costly and time consuming because it incorporates several screening and confirmatory steps. In addition, performance of the LA scheme requires highly trained lab specialists.²⁰ A study comparing testing for coagulation disorders prior to warfarin treatment compared with no testing and treatment with warfarin in patients with ischemic stroke revealed a significant change in incremental cost-effectiveness ratio (ICER) among the patients who were not tested.²¹ Although this observation was based on an additional health care intervention, whose value may be a debatable in a resource limited setting, the financial burden attributable to inappropriate requisition appears to be of no benefit to patient care. It is therefore

**Figure 1.** Reasons for lupus anticoagulant test requests that do not meet ISTH indications.

mandatory that strategies be implemented for optimizing proper patient selection for specialized coagulation testing.

CONCLUSION

The lupus anticoagulant test was inappropriately requested by a high proportion of clinicians, indicating poor adherence to the recommended algorithm. Similarly, a vast majority of improper requests were related to anticoagulant therapy, which highlights the importance of implementation of a comprehensive diagnostic algorithm for patients on warfarin and heparin therapy. This practice, though contrary to the recommended guidelines, not only contributed to avoidable workload on laboratory resources, but was also not cost effective. These observations highlight the importance of implementing recommended guidelines and better collaboration between clinicians and laboratory staff.

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