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Pathology

KEY WORDS:

COST-BENEFIT ANALYSIS OF THE PRELIMINARY STEP PRIOR TO CLASSICAL LUPUS ANTICOAGULANT DETECTION ASSAYS

Dr. Mansour S Aljabry

Pathology department King Khalid University Hospital –King Saud University Kingdom of Saudi Arabia P.O Box2925, Riyadh11461

ABSTRACT

Background: The classical panel of lupus anti-coagulant (LA) test involves a number of cumbersome and expensive assays. Proper patient selection by introduction of a preliminary step prior to classical panel of LA may be a cost-benefit approach.
Objectives: This study was performed to evaluate the cost benefit of the preliminary step prior to full panel LA test.
Design: This retrospective study was performed in coagulation laboratory from February 2013 to February 2015.
Setting: This study was performed in coagulation laboratory at King Khalid University Hospital.
Patients and Methods: An algorithm for LA test was designed according to the ISTH guidelines. It involved introduction of a preliminary step comprising of INR, thrombin time (TT) and fibrinogen assay to be performed on all LA requisitions prior to classical LA test. Any LA test request with high TT (>16 seconds) or high INR (>1.5) or low fibrinogen (<1.2 g/l) was considered invalid request and the sample was not subjected to the classical LA assays. LA requests with normal TT, INR and fibrinogen levels were considered valid request in which the classical LA panel were performed.
Main Outcome Measures: The following equation was used to obtain the net cost-benefit:
Net cost-benefit =Total earned benefit obtained from the excluded requests - Cost of preliminary step of all requests.
Results: A total of 417 lupus anticoagulant requests were received in coagulation laboratory. 329 (78.9%) were valid requests whereas 88(22.1%) were invalid requests and only the preliminary step were carried out. The net saving generated from adding of the preliminary step to the LA test was 13973.3 USD.
Conclusions: Preliminary step prior to classical LA assays is a substantial cost-benefit approach for proper utilization of laboratory resources. Moreover, it rectifies the improper requisition of highly specialized and costly coagulation tests.

BACKGROUND AND OBJECTIVES

LA test is essential for the diagnosis of antiphospholipid syndrome (APS) characterized by arterial or venous thrombosis and pregnancy complications.[1,2] The test comprises of a group of assays which detect heterogeneous autoantibodies that interfere with phospholipid dependent coagulation assays. Detection of LA is a complex and challenging procedure not only because of the variability in antibody specificity but also due to the differences among reagents, analyzers and testing strategies.[3] A number of guidelines for development of a gold standard algorithm have been put forward for LA testing.[4-6] Despite variations among the published guidelines there has been a complete consensus that none of the available assays can detect LA accurately. Reliance on a panel of different assays for detection of LA therefore continues. Classical LA detection is based on screen-mix-confirm approach according to almost all guidelines. Proper patient selection for LA detection is a crucial step in order to avoid the risk of obtaining false-positive results due to poor specificity of the LA assays.

LA panel testing is not only expensive but is also time consuming and labor intensive investigation requiring highly skilled laboratory specialists.[7] In a resource limited laboratory it may prove to be a major constrain particularly when the test requisitions are not in conformity with the recommended guidelines. Requisition of LA test for patients receiving warfarin or therapeutic doses of unfractionated heparin may yield false positive result because of the drug induced prolongation of clotting times.[4,6] Warfarin and heparin therapy is among the leading causes of inappropriate laboratory requisitions for LA testing and is an avoidable constraint on laboratory resources.[8] Similarly congenital or acquired hypofibrinogenemia assay may interfere with accuracy of LA test by inducing prolongation of base line coagulation.[9]

In accordance with the ISHT guidelines introduction of preliminary step prior to the classical LA assay for LA appears to be a useful intervention for avoidance of inappropriate LA requisition. However, the introduction of preliminary step prior to classical LA tests is liable to incur additional expenses for not being a component of full panel LA tests. This study was performed to assess the cost and benefit of the preliminary step prior to classical LA tests.

PATIENTS AND METHODS

This retrospective study was conducted in the coagulation laboratory at King Khalid University Hospital Riyadh. All LA requests received between February 2013 and February 2015 were included in the study.

Procedure:

The preliminary step prior to classical LA tests was designed to minimize inappropriate requisition for LA according to the ISTH guidelines. The preliminary step comprised of INR (STA-R; Diagnostica Stago), TT (STA-R; Diagnostica Stago) and fibrinogen assay (STA- Clauss method; Diagnostica Stago). This preliminary step was performed on all LA requests prior to classical LA test. Any LA request with high TT (>16 seconds) or high INR (>1.5) or low fibrinogen level (<1.2 g/l) was deemed as invalid request and the sample was not subjected to the classical LA test. LA requests with normal thrombin time, INR and fibrinogen levels were considered valid for classical LA panel testing. The classical LA panel included screening, mixing study and confirmatory step. Screening step compromised of Dilute Russell's Viper Venom Time-screen (DRVVT-s) and Activate Partial Thromboplastin Time-LA (PTT-LA) while confirmatory step consists of DRVVT-c and STACLOT- LA (Diagnostica Stago). The cut-off for INR was taken from the ISTH guideline while the cut-off for thrombin time and fibrinogen assay were the reference range limits.

Cost of each step was estimated by calculation of the price for all assays incorporated in that step and estimation of the staff fare as well (**Tables 1 and 2**).

Cost of the preliminary step for all LA requests was calculated by USA Dollar (USD). The net saving generated by exclusion of invalid LA requests was also estimated in the similar manner. Finally, the cost benefit analysis was performed by subtraction of total cost of the preliminary step from the total earned benefit obtained from excluded LA requests.

Data Collection:

Data for 417 LA request were recorded in data collection form specifically designed for the study using an Excel sheet (Microsoft 2010). Details regarding patient demographics, clinical findings and the requesting department were recorded.

Statistical analysis:

A descriptive statistics was used to obtain percentages, median age, cost and benefit. The following equation was used to obtain the net cost-benefit:

Net cost-benefit = Cost of preliminary step of all requests – Total earned benefit obtained from the excluded requests.

The expression of the result was in Saudi Riyal and USA dollar.

Research approval:
This study was approved by the Institutional Review Board (IRB), of the College of Medicine, King Saud University.

RESULTS

During the study period a total of 417 LA requisitions were received in coagulation laboratory. This group of patients included 59.7% females and 40.3% males with the median age of 48.4 years (**Table 3**). After the preliminary step 329 (78.9%) LA requests were considered valid and were subjected to classical LA testing. There were 88 (22.1%) invalid requests and only the preliminary step was performed for these requisitions.

The most common reason for the invalid requests was high INR due to warfarin therapy in 48 (54.56%) patients followed by high thrombin time due to heparin therapy among 37 (40%) patients and the least common reason was low serum fibrinogen level in 3 (3.4%) patients.

The total cost of the preliminary step of all LA requests was 4,448 USD while the total amount of the earned benefit obtained from the excluded invalid LA requests was 18,418USD. The net saving generated from adding of the preliminary step to the LA test was 13,970 USD (**Table 4**).

DISCUSSION

Introduction of preliminary step prior to classical LA testing was a substantial cost-benefit approach and saved about 52,400 SAR (14,208 USD). The main factor contributing to higher expenses associated with LA testing is the performance of series of laboratory assays because of lacking a single test that could detect all kinds of Las.[10] Among a number of strategies investigated for making LA testing, a two-step approach involving a preliminary step prior to full panel LA testing has been shown to be a cost effective method.[11] ISTH guidelines recommend performance of at least two screening tests prior to full panel LA testing. The two tests recommended by ISTH guidelines are Dilute Russell Viper Venom Time (DRVVT) test and aPTT based assay for being highly sensitive and specific screening tests for LA.[7] Both DRVVT and aPTT based assay are expensive tests and the expenses associated with these tests may vary as the cost of LA reagents is inversely proportional to the volume of the workload.[12,13] Relatively higher cost of LA test in our laboratory was most likely due to the low to moderate workload and using DRVVT and aPTT-LA reagents.

A sizable proportion (21.1%) of invalid requests was found to be an additional avoidable burden on the laboratory resources in the present study. This observation indicates poor compliance to the recommended guidelines for LA testing. Although lack of compliance to guidelines is multi-factorial however, it remains a major cause of invalid requisitions.[10] Other common causes of invalid requisitions include improper requisition forms, poor communication between laboratory staff and the requesting clinicians and lack of adequate knowledge.[14-17] Presence of warfarin in the test sample compromises the quality of LA detection assays, with holding warfarin and substitution with low molecular weight heparin is recommended under such conditions.[4,18] More than half of the invalid requests in the present study were due to warfarin therapy a finding consistent with non-compliance to ISTH guidelines. Moreover, a higher degree of compliance to guidelines for LA detection has been shown to be associated with a significant improvement in performances of LA detection assays.[19]

High thrombin time due to heparin therapy represents 42% of the invalid requests while low fibrinogen is the least common representing 3.4%. This finding indicates the importance of adding of thrombin time and fibrinogen assay prior to the classical LA test not because of cost issue only, but because of quality of LA test. According to the guidelines, therapeutic dose of heparin and low fibrinogen level compromise the quality of LA testing and may qualify patients to prolonged unnecessary anticoagulant treatment.[5,6]

In the present study, various medical departments and outpatient clinic are involved in requisition of the invalid requests including hematology (18.2%), cardiology (15.9%) and surgery (14%). This finding indicates that poor compliance to the recommended guidelines is not confined to a specific medical team but involve multidisciplinary team. Presence of such short coming emphasis on significance of establishment of the preliminary step prior the classical LA assay. On the other hand, it points toward the effect of insufficient requests forms and lack of electronic requisition forms. Electronic forms obligate the clinician to furnish the request with the most relevant data such as drug history.[17]

Although performance of INR, TT, and fibrinogen prior to any LA request appears to be cost effective approach, however, it increases the workload on routine coagulation tests. This intangible cost cannot be estimated accurately as it includes unmeasurable extra burden to the staff, reagent and to laboratory automated analyzers.

New oral anticoagulant such as Dabigatran and Rivaroxaban effect the accuracy of LA test and lead to frequent false positive results.[19] However, their effect on LA testing has not been addressed in this study due to lack of proper monitoring assays for such new drugs in our laboratory.

CONCLUSION

Preliminary step prior to classical lupus anticoagulant assays is a cost-benefit approach that helps in proper utilization of laboratory resources. Moreover, it rectifies the improper requisition of highly specialized and costly coagulation tests. This study confirms the key role of pathologists in guiding the most cost-benefit testing strategies for laboratory tests in order to maximize the benefit with simultaneous reduction of the cost.

Table 1. Cost of the preliminary step.

Test	aPTT	INR	Thromb in time	Fibrinogen	Staff fare	Total cost
Price(USD)	1.33	1.33	6.66	1.33	Non (fully automated)	10.6

Table 2. Cost of classical lupus anticoagulant assays.

Test	aPTT& Mixing study	Thromb in time	aPTT-LA &Staclot-LA	DRVVT-s & DRVVT-c	Fibrin ogen	Staff fare	Total cost
Price (USD)	16	1.6	61	104	1.3	20	210

Table 3. Requests for lupus anticoagulant testing.

Type of requests	Number	Female	Male	Median age
All requests	417	249(59.71%)	168(40.29%)	48.4 years
Valid requests	329(78.9%)	198(60.18%)	131(39.82%)	47.2 years
Invalid requests	88 (21.1%)	47(53.4%)	41 (46.6%)	50.3 years

Table 4. Cost and benefit calculations.

Type of incurred cost	Number	Cost per request (USD)	Total amount (USD)
Cost of all requests	417	209.3	87,292
Cost of all preliminary step	417	10.6	4,448
Saving from excluded Invalid LA requests	88	209.3	18,418
Net saving (saving from excluded LA requests– Cost of preliminary step)			13,970

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