Laboratory identification of Lupus Anticoagulants Using the Combination of Activated Partial Thromboplastin Time and Russell's Viper Venom at Two Phospholipid Concentrations

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Abstract

The most appropriate combination of tests for lupus anticoagulants (LA) is unknown. The standard double centrifugation method to prepare plasma was inadequate for platelet elimination, interfering with kaolin clotting time and mixing studies. In the present study, the percentage correction of activated partial thromboplastin time (APTT) and Russell's viper venom time (RVVT) by high compared with low concentrations of phospholipid was used for both screening and confirmation of LA. Abnormality in either one was reported as positive. The specificity of the tests in 122 individuals without LA was 100 per cent for RVVT and 96.7 per cent for APTT, which yielded false positive by heparin. The mixing study was omitted from the authors' strategy without decreasing the specificity. In 795 patients with thrombosis, LA was detectable in 6.03 per cent. The sensitivity of diluted activated partial thromboplastin time (dAPTT) and diluted Russell's viper venom time (dRVVT) alone, compared with the combination of the two was 83.3 per cent and 79.2 per cent respectively. Therefore, this new test scheme is a simple, inexpensive and efficient method for Thai patients.

Key word : Lupus Anticoagulants, Laboratory Identification, APTT, RVVT

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Antiphospholipid syndrome is an autoimmune disorder causing thrombosis and/or pregnancy loss. Identification of the patients with this syndrome is essential, as they possess a very high risk of recurrent thrombosis requiring a long-term and high-intensity anticoagulant[1]. Notably, this autoantibody paradoxically interferes with *in vitro* coagulation resulting in prolonged coagulation tests. This phenomenon, termed lupus anticoagulants (LA), has been clinically useful as a blood test for this thrombophilic condition. Although the antiphospholipid is also detectable using Enzyme Link Immuno Sorbent Assay (ELISA) methods for anticardiolopin antibody, the LA test is more predictive for thrombosis[2,3] and, hence, should be performed in all patients suspected of having antiphospholipid syndrome.

The Scientific and Standardization Committee (SSC) of the International Society on Thrombosis and Haemostasis (ISTH) defined a stepwise guideline for the diagnosis of LA as 1) Screening test: prolongation of phospholipid-dependent coagulation test, 2) Mixing test: uncorrectable by a mixing test suggesting an inhibitor activity, 3) Confirmatory test: neutralization of the inhibitory effect by addition of excess phospholipid, 4) Exclusion of the coagulation factor inhibitors[4,5]. There is no single 'gold standard' test for LA. Therefore, these diagnostic criteria are based on a consensus from an expert panel. Although the criteria are rigorous and suitable for classification of patients in clinical trials, it is still impractical and may not be cost-effective in clinical practice[6].

The definition of uncorrectable mixing study was not defined in SSC-ISTH criteria. Nevertheless, it is important that all platelets be removed from normal plasma before mixing study because platelets are the source of phospholipid. After freezing and thawing normal plasma, residual platelets may release phospholipid masking the lupus inhibitor during the mix[7,8]. The best way to prepare platelet-free plasma is filtration through 0.22 mM filter[8]. Due to the high cost of the filter, double-centrifugation method is commonly used to eliminate remaining platelets.

Recently, the determination of the ratio of the activated partial thromboplastin time (APTT)-based coagulation time with high and low phospholipid, called lupus ratio[9], has been used more widely. An abnormally large difference between the two values, indicating the phospholipid dependency, suggests the diagnosis of LA. This method was simplified by combining a screening test, a mixing study and a confirmatory test into one. It has been shown to be more sensitive than the conventional methods[10], in which the confirmatory test is used only after the screening test is positive. In addition, the lupus ratio has been found to be reproducible among different laboratories[11]. Furthermore, a recent report has successfully used a Russell's viper venom time (RVVT)-based ratio to detect LA in patients taking oral anticoagulant[12].

For LA diagnosis, a combination of coagulation tests is required for sufficient sensitivity and specificity. There is a variety of screening tests and confirmatory tests for LA. However, only APTT-based assay[2] and RVVT[3] have been shown to have better clinical correlation than anticardiolipin ELISA tests. The objective of this study was to explore the combination of APTT and RVVT-based methods, each performed at 2 phospholipid concentrations, as a diagnostic test set for LA. The tests at low concentration (as screening) and at high concentration (as confirmatory) were performed simultaneously instead of sequentially for time-saving. In addition, the mixing study was omitted to save the cost of plasma filtration. The test was also performed on 77 normal subjects and 45 APTT-prolonged patients without LA to determine whether the specificity of the test was compromised without mixing study. In the present study, the authors also showed clinical uses in a large number of thrombotic patients.

MATERIAL AND METHOD

Subjects

1. Normal subjects (n = 77) were healthy medical personnel and medical students with no history of bleeding tendency. They all had normal APTT and PT values.

2. Patients with prolonged APTT due to various causes other than LA (n = 45).

   a. Cirrhosis (n = 8).

   b. Oral anticoagulant (OAT) (n = 11).

   c. Coagulation inhibitor (Factor VIII inhibitor) (n = 6).

   d. Unfractionated heparin (n = 11).

   e. Coagulation factor deficiency (n = 9).

3. Patients with known LA positive diagnosed by the conventional method, i.e. dilute APTT screening, mixing study and confirmatory platelet neutralization procedure[13] (n = 10).

4. Patients with confirmed thrombosis and/or pregnancy loss suggesting a possibility of antiphospholipid syndrome (n = 795).

Specimen collection and processing

Blood was drawn using the two-syringe technique with 21 gauge needles. The anticoagulant was 0.109 mM trisodium citrate at 1 : 9 (anticoagulant: blood) ratio[14]. Normal subjects and patients without LA (subject 1 and 2) had blood drawn by the first author or other experienced personnel in the Hematology division. Oral informed consent was made before specimen collections. The patients (subject 3 and 4) had blood drawn by referring physicians or medical students. All were instructed regarding correct specimen collection both in class and by written instructions. Specimens with too-low volume or hemolysis were excluded. Double centrifugation at room temperature was used for all plasma samples. Blood was first centrifuged at 1,000 x g for 10 minutes. The plasma was then transferred to a fresh Eppendorf tube and re-centrifuged at 10,000 x g for 10 minutes. Fresh plasma was tested immediately. Otherwise, plasma was frozen at -80°C until tested. Before testing, frozen plasma was thawed at 37°C.

Laboratory tests

1. Kaolin Clotting Time (KCT) was performed according to the method of Exner et al[15].

2. diluted Russell's Viper Venom Time (dRVVT) was modified from Thiagarajan et al[16, 17]. Russell's viper venom (Diagnostic Reagents, Thame, Oxon, UK) was dissolved in distilled water at 0.1 mg/ml final concentration. It was then diluted (1 : 1,000) with Imidazole Buffer Saline (IBS) pH 7.3 or by adjusting the RVV clotting time to 30-40 sec.

The test was performed at 2 phospholipid concentrations (20-fold difference). The phospholipid source was from Bell and Alton Platelet Substitute (Diagnostic Reagents, Thame, Oxon, UK).

a. Low concentration: phospholipid was dissolved according to the manufacturer's instructions and then further diluted 1 : 10 with IBS.

b. High concentration: phospholipid was dissolved at half of the recommended volume.

3. Diluted APTT (dAPTT)[17] was also performed at 2 phospholipid concentrations and composed of

a. One part of 2.5 mg/ml light kaolin in IBS.

b. Phospholipid preparation (low or high concentration) as described above.

c. One part of citrated plasma.

The mixture was warmed at 37°C for 5 minutes.

d. Add 1 part of pre-warmed 0.025 M $CaCl_2$ and record the clotting time.

All coagulation tests were performed manually in duplicate. The average values were then subtracted with the values of the pooled normal plasma performed on the same day to calculate the ratio. The ratio L and ratio H were from tests in low and high phospholipid concentrations respectively. The percentage of correction was then derived from the formula.

$$\text{Percentage of correction (\% Correction)} = \frac{\text{Ratio L - Ratio H} \times 100}{\text{Ratio L}}$$

Table 1. Means ± standard deviations of the clotting times (second) performed in fresh and previously frozen plasma (n = 27).

	Fresh plasma	Frozen plasma
KCT	95.05 ± 9.94	67.96 ± 16.77
dAPTT (low phospholipid)	53.99 ± 4.54	47.11 ± 4.32
dAPTT (high phospholipid)	52.14 ± 4.25	50.40 ± 4.25
dRVVT (low phospholipid)	44.59 ± 3.67	40.88 ± 2.89
dRVVT (high phospholipid)	51.64 ± 6.99	45.37 ± 3.45

RESULTS

The LA tests will be more practical, if they can be performed in either fresh or previously frozen plasma. However, broken platelets contaminating the sample after freezing and thawing may interfere with the tests. KCT and dAPTT are the most popular screening tests for LA. The authors, therefore, compared KCT, dRVVT and dAPTT of fresh samples with those of previously frozen samples. Plasma was collected from 27 normal individuals followed by double centrifugation. As shown in Table 1, KCT was markedly shortened in previously frozen plasma, compared with fresh plasma. If KCT is used as a screening test, the sensitivity for LA detection will be considerably reduced. In contrast, RVVT and APTT values at either high or low phospholipid concentrations were modestly affected after freezing and thawing. The differences of the clotting time between fresh and frozen specimens of APTT and RVVT were significantly less than that of KCT ($p < 0.000001$, paired *t*-test).

The authors initially optimized the concentrations of phospholipid. The dAPTT was performed on normal plasmas at varying concentrations of phospholipid. The curve plotting between phospholipid concentrations and clotting times were parabolic i.e. the clotting time was shortest at the manufacturer-recommended phospholipid concentration, but progressively prolonged above and below that point (data not shown). The 20-fold difference in concentration (2-fold concentrated *vs* 1 : 10 diluted relative to the recommended concentration) was selected as it yielded clotting times that were fairly close together (Table 1). Percentage of differences in clotting times from both dAPTT and dRVVT were then calculated and reported as percentage of correction. (% correction)

In normal subjects (n = 77), the two clotting times at high and low phospholipid concentrations do not significantly differ (Fig. 1 and 2). The means ± standard deviations of per cent correction were -3.38 ± 9.62 per cent for dAPTT and -4.16 ± 7.38 for dRVVT. This suggests that the phospholipid concentrations the authors used were optimal. However, a clotting time at higher phospholipid concentrations is usually shorter than that at lower concentrations in patients with LA. According to the maximal percentage correction detectable in normal subjects, the authors defined the cut-off values for LA test using dAPTT and dRVVT as 14 per cent and 11 per cent respectively. To enhance the sensitivity, results of both tests were considered. LA was reported positive when the per cent correction of one or both tests exceeded these cut-off points.

To investigate the specificity, the tests were then performed in patients with prolonged APTT due to causes other than LA (n = 45). These included liver cirrhosis, hemophilia A or B, factor VIII inhibitor, and patients taking heparin or an oral anticoagulant. In the dRVVT test, none of these conditions gave false positive LA (Fig. 2). In dAPTT test, all but 4 cases in the heparin group also yielded negative results. To exclude a false positive caused by heparin, the authors also performed a heparin-sensitive thrombin time (TT) in all cases with positive LA. If dAPTT was positive, but dRVVT was negative and TT was prolonged, the possibility of heparin effect was also reported to the clinicians.

The test was then performed in 795 consecutive patients with thrombosis and/or pregnancy loss to evaluate effectiveness of the test in practice. Forty-eight (6.03%) showed positive LA using the authors' method. Within the LA positive group (n = 48, counted as 100%), dAPTT was positive alone in 20.8 per cent, dRVVT was positive alone in 16.7 per cent and both tests were positive in 62.5 per cent.

DISCUSSION

In the present study, the authors adopted the SSC-ISTH guideline for laboratory diagnosis of LA and adapted the test to be more practical and economical. The ratio of clotting time between high and low phospholipid combined the screening and confirmatory test for simplicity. Both APTT-based and RVVT-based methods have previously demonstrated to be clinically relevant and the authors show here that they may be performed on previously frozen plasma. Utilizing dilutions of phospholipid as the screening part of the test, dAPTT and dRVVT, has been shown to enhance the sensitivity of LA detection[17,18]. All reagents are well defined and the mixture can be prepared with low unit cost.

Double centrifugation is the most economical way to prepare plasma samples for LA tests. This method is still recommended as a standard plasma preparation for LA test by an expert[19]. However, the present findings indicate that double centrifugation cannot adequately eliminate residual platelets resulting in false negative results. The effect is more pronounced in KCT, which is a widely-used screening test for LA. From the presented data, KCT must

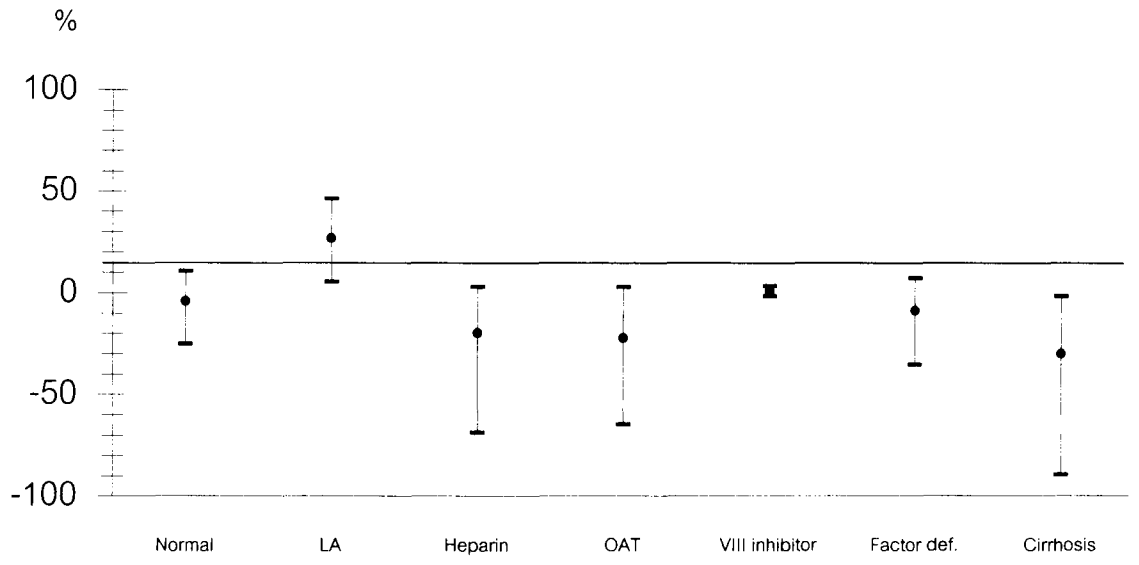

Fig. 1. Percentage of correction of RVVT at low and high phospholipid concentrations from each group plasma samples was obtained. The points represent the mean and the upper and lower bars represent maximal and minimal values respectively. The horizontal line across the graph is the upper limit of normal derived from the maximal values of the normal individuals.

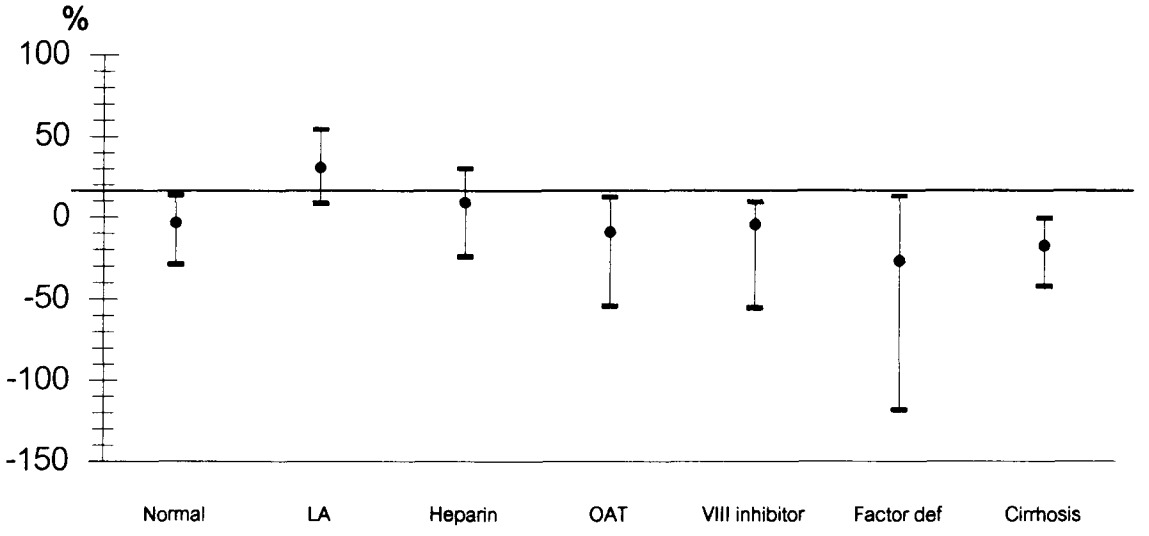

Fig. 2. Percentage of correction of APTT at low and high phospholipid concentrations from each group of plasma samples was obtained. The points represent the mean and the upper and lower bars represent maximal and minimal values respectively. The horizontal line across the graph is the upper limit of normal derived from the maximal values of the normal individuals.

be performed only in fresh samples because it is very sensitive to methods of plasma preparation. Another implication from this result is to confirm that pooled normal plasma for mixing study requires filtration (20,21). Consistent with the presented result, another study in Thailand using double-centrifugation for plasma preparation found that mixing study revealed negative results (correctable) in some patients with LA(22). It is clear from the presented data that the incorporation of mixing study in the test strategy without filtered plasma will reduce the test sensitivity. Therefore, a large-scale comparison between the presented test and the LA test containing mixing study was not performed. Nevertheless, the presented test detected LA in all the patients with known LA by the conventional method.

The purpose of the mixing study is to exclude the false positive LA by clotting factor deficiencies. To determine whether omission of the mixing study decreased the specificity of the tests, the authors performed LA tests in patients with factor deficiencies, cirrhosis and patients taking oral anticoagulants. None of them showed false positive results of LA suggesting that the mixing study is not absolutely essential for LA testing in clinical practice. Without the mixing test, 2-3 hours of work can be saved. In addition, the unit cost can be reduced by approximately 110 baht per test (Filter cost: 70 baht, Preparation of pooled filtered plasma for mixing: 40 baht).

In the presented tests, phospholipid was used instead of platelets in the confirmatory test because, platelet preparations gave greater lot-to-lot variations. In addition, platelets contain not only phospholipid, but also platelet factor 4 and factor V. These factors can neutralize heparin and anti factor V respectively and theoretically cause false positive LA in these conditions(23). Although RVVT-based method is one of the most important screening and confirmatory tests for LA, variation in phospholipid sources is a cause of variable results(24). Therefore, a similar well-defined phospholipid source was used for all tests in the presented scheme.

The maximal per cent correction from normal volunteers was used to set a cut-off point of phospholipid dependency. The dRVVT test yielded 100 per cent specificity in 122 individuals (77 normal subjects and 45 cases with prolonged APTT from other causes). Only heparin administration caused false positive results in the dAPTT test, resulting in a specificity of 97.6 per cent. If thrombin time is also prolonged, the possibility of heparin effect has to be considered. Clinicians can exclude this possibility easily using history taking. Low molecular weight heparin is unlikely to interfere with the test because, in contrast to standard heparin, it usually does not prolong APTT. According to the fourth criteria of SSC-ISTH, coagulation factor inhibitor needs to be excluded. In clinical practice, coagulation factor assays are not routinely done. It is only performed when there is a suspicion of a specific factor inhibitor (19). However, the presented LA tests did not yield any false positive in 6 patients with factor VIII inhibitor.

The rate of detection of LA in 795 thrombotic patients was 6.03 per cent, which is comparable to a recent report in 278 Thai patients (4.3%)(22). This report from another laboratory used a combination of 4 screening tests, a mixing study and 3 confirmatory tests. In the present study, the positive rates of dAPTT alone and dRVVT alone were 83.3 per cent and 79.2 per cent compared with the combination of 2 tests, underscoring the advantage of using the combination of 2 tests to increase the sensitivity. In addition, this supports the fact that anti-phospholipid antibodies are heterogeneous groups of immunoglobulins(25,26). Each group may require a different test for detection. It remains to be determined whether addition of other tests can enhance the sensitivity of LA detection.

In conclusion, a method of LA detection has been developed based on the dRVVT and dAPTT methods at 2 phospholipid concentrations. The screening and confirmatory tests are performed simultaneously to save time. The mixing study is omitted to save cost and time without decreasing the specificity. It also possesses an acceptable positive rate. No special instrument is required. It can be used in any coagulation laboratory in Thailand.

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การใช้วิธี Diluted Activated Partial Thromboplastin Time ร่วมกับ Diluted Russell's Viper Venom Time ในการวินิจฉัย Lupus anticoagulants

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การวินิจฉัย Lupus anticoagulants (LA) ต้องอาศัยการตรวจเลือดหลายชนิดร่วมกันซึ่งปัจจุบันยังไม่มีข้อสรุปว่าควรจะเลือกการตรวจใดบ้าง พบว่าการเตรียมพลาสมาโดยการปั่น 2 ครั้งนั้นไม่เพียงพอในการกำจัดเกร็ดเลือดให้หมดไปจึงรบกวนการตรวจ Kaolin Clotting time และ ขั้นตอนการผสมกับพลาสมาปกติ (mixing study) ส่วน Activated partial thromboplastin time (APTT) และ Russell's viper venom time (RVVT) ถูกรบกวนน้อยกว่า ในการศึกษานี้ ได้รวมการตรวจกรองและการตรวจยืนยันเป็นการตรวจเดียว คือการตรวจ APTT และ RVVT โดยตรวจที่ความเข้มข้นของฟอสโฟลิปิดแบบเจือจางและเข้มข้น ถ้าการแข็งตัวของการตรวจอันใดอันหนึ่งสั้นลงมากกว่าปกติด้วยการเพิ่มความเข้มข้นของฟอสโฟลิปิดจะแสดงว่ามี LA ส่วนขั้นตอนการผสมกับพลาสมาปกติ (mixing study) ได้ถูกตัดออกไป โดยไม่ทำให้ความจำเพาะของการตรวจลดลง พบว่าความจำเพาะของ diluted Russell's viper venom timed (RVVT) และ diluted Activated partial thromboplastin timed (APTT) เป็น 100% และ 96.7% ตามลำดับ ผลบวกเทียมในการตรวจ dAPTT ทั้งหมดเกิดจากผู้ป่วยที่ได้รับเฮปาริน ต่อมาการตรวจนี้จึงได้นำไปใช้ในผู้ป่วยลิ่มเลือดอุดตัน 795 ราย โดยพบ LA 48 ราย (6.03%) ซึ่งใกล้เคียงกับรายงานอื่นในผู้ป่วยไทย ความไวในการตรวจ dRVVT และ dAPTT ตัวเดียวเมื่อเทียบกับใช้ 2 ตัวเป็น 79.2% และ 83.3% ตามลำดับ จึงสรุปว่าการตรวจใหม่นี้ทำได้ง่าย ราคาถูก และได้ผลดีในการตรวจหา LA ในผู้ป่วยไทย

คำสำคัญ : ลูปัส แอนติโคแอกกูเลนท์, การตรวจทางห้องปฏิบัติการ, APTT, RVVT

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