A Survey of Coagulation Laboratory Practice in Thailand: the First Step to Establish a National External Quality Assessment Scheme (NEQAS) for Blood Coagulation

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Background: *External quality assessment (EQA) is an essential component of laboratory quality assurance. In Thailand, there is no EQA program for coagulation tests at the national level.*
Objective: *To collect the necessary data in the first step to set up a National External Quality Assessment Scheme (NEQAS) and to assess the status of coagulation laboratory practice in Thailand.*
Material and Method: *Questionnaires were sent to hospitals to obtain information about the hospitals, their coagulation laboratory practice and EQA.*
Results: *From a dispatch of 220 questionnaires, 124 (56.4%) were returned. Of the 112 hospitals that had coagulation tests, all of them performed prothrombin time (PT), and 110 laboratories performed activated partial thromboplastin time (APTT) as well. Thirty eight percent of laboratories still used 3.8% sodium citrate as the anticoagulant for coagulation tests. The majority of laboratories (65%) reported normal control value with the patient results. Only 42% of coagulation laboratories established their own reference range. The denominators of PT ratio and APTT ratio calculations were derived from several sources apart from the mean of normal subjects. Seven of 112 (6%) laboratories participated in an EQA program.*
Conclusion: *The present survey represents an overview of the current laboratory practice for coagulation tests in Thailand. Improvement is necessary, and the survey results emphasize the need for establishing an EQA program in Thailand.*

Keywords: *External quality assessment, Coagulation tests, Survey*

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External quality assessment (EQA) is an essential component of laboratory quality assurance. Its primary function is to test the competence of individual laboratories by analysis of the degree of agreement between one laboratory's results and other participants. In medical laboratories, the scope for the use of EQA is usually becoming broader than in other laboratory fields. Education and help are included in the goals of EQA as well, which can lead to the improvement of laboratory performance and finally optimal patient care[1]. In Thailand, there are EQA programs for chemistry and hematology at the national level. Unfortunately, there is no scheme for coagulation tests that are useful for screening and diagnosis of inherited and acquired bleeding and thrombotic disorders as well as for monitoring of anticoagulant controls. Monitoring is particularly important since under dosage can cause thrombosis and over dosage can lead to bleeding; both complications may be associated with fatal outcomes.

The authors' laboratory, the Department of Clinical Pathology, Faculty of Medicine, Siriraj Hospital, is a member of WHO International External Quality Assessment Scheme for Blood Coagulation (WHO IEQAS), the purpose of which is not only to provide

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EQA for tests of hemostasis but also to promote high standards of laboratory performance and practice. Additionally, the aim is to encourage participants to establish, where not already instituted, National External Quality Assessment Scheme (NEQAS) within their own country.

For these reasons, the authors intend to establish a NEQAS to improve the performance of coagulation laboratories in Thailand. However, there are many factors that have to be considered apart from the reagents and instruments[2,3], such as the pre-analytical phase; anticoagulant used for blood collection[4], the establishment of reference ranges, and the reporting system. Accordingly, the authors sent questionnaires to the hospitals expected to perform coagulation tests. This was the first step to collect the necessary data to set up NEQAS and to assess the status of coagulation laboratory practice in Thailand.

Material and Method

In May 2005, two hundred and twenty questionnaires were sent to provincial and regional public hospitals, as well as university hospitals, and large private hospitals to obtain information on three main topics as follows:

Data on the hospitals

1. Public or private
2. Number of beds

Data on coagulation tests

1. What coagulation tests are performed in the laboratory? (e.g.: prothrombin time (PT), activated partial thromboplastin (APTT), thrombin time (TT), etc.)
2. What is the anticoagulant used for blood collection for coagulation tests?
3. What are the names of reagents used for PT, APTT and TT?
4. What is the instrument used for coagulation tests?
5. Are the patient results reported with the reference range, therapeutic range or with normal control value?
6. How is the reference range obtained or derived?
7. How are the denominators used for PT ratio in the International Normalized Ratio (INR) calculation, or APTT ratio derived?

Data for EQA

1. Is there any EQA for their coagulation tests?
2. Will they participate in NEQAS? If they would like to, can they afford the membership fee of 2,000 baht per year?

After the return of questionnaires and knowing that some laboratories report APTT ratios for monitoring of heparin therapy, telephone interviews were randomly made to confirm the data and to obtain the data about the use of unfractionated heparin in the hospitals. The results were presented in the form of frequency tables and pie diagrams with number and percentage distribution.

Results

Hospital characteristics

From a dispatch of 220 questionnaires, 124 (56.4%) were returned. Twelve hospitals performed no coagulation tests. Interestingly, among these hospitals, there were two hospitals that had 200 beds and one hospital that had 670 beds. Of the 112 hospitals that had coagulation tests, 85 (75.9%) were public and 27 (24.1%) were private hospitals. Their bed capacities are shown in Table 1.

Tests for service

All of 112 laboratories performed PT as well as INR. However, the number of laboratories that performed APTT was 110 (two hospitals with 420 and 508 beds did not perform APTT). Only 32 (29%) of 110 laboratories reported APTT ratio. Telephone interview of 20 (26%) technicians in 78 laboratories that did not report APTT ratio revealed that unfractionated heparin therapy was used in 12 of these hospitals. However, the clinicians did not request an APTT ratio for heparin dosage monitoring. The means by which heparin dosage monitoring occurred in these hospitals was not known by the laboratory staff. In the other eight hospitals, the technicians did not know whether heparin therapy

Table 1. Number of beds in the hospitals that returned questionnaires

Number of beds	Number of hospitals (%)
80-200	19 (17.0)
201-400	37 (33.0)
401-600	23 (20.5)
601-800	11 (9.8)
801-1000	9 (8.0)
1001-1800	5 (4.5)
No answer	8 (7.1)
Total	112 (100)

was administered in their hospitals. Thirty-seven (33%) of 112 laboratories performed the thrombin time (TT), which measures fibrinogen indirectly.

Types of anticoagulant

Types of anticoagulant used for blood sample collection are shown in Fig. 1. A few laboratories did not give this information.

Reagents and instruments

The uses of at least 17 different PT reagents, 13 different APTT reagents and 17 different instruments were reported. The most commonly used reagents were Thromborel S and Actin FS for PT and APTT, respectively (Table 2).

Results of reporting systems

It was noteworthy that the majority of laboratories (around 65%) reported normal control value with the patient results (see Fig. 2).

The presented questionnaire results revealed that 17 (15%) laboratories reported INR together with PT in seconds in all cases and two laboratories also reported% activity of PT. Therapeutic INR ranges were reported together with the INR value in nine laboratories; six of them used INR of 2-4, the others used 1.5-4.5, < 3, 4-5. None of the laboratories reported a therapeutic range of APTT for heparin monitoring.

Sources of reference (range and denominator)

The sources of reference range are shown in Fig. 3. Only 48 of 112 laboratories (42%) established their own reference range for PT. However, only 21 of these 48 (44%) laboratories did this for every change of reagent lot. The proportion was similar for APTT: 47 of 110 laboratories established their own reference range, and 21 out of 47 did it for every change of reagent lot.

The sources of denominators used for the calculation of INR and APTT ratio are displayed in Fig. 4.

Participation in EQA

Seven of 112 (6%) laboratories participated in an EQA program, with 6 of them participating in the Asian Quality Assurance Survey Program (AQUAS). One laboratory participated in two EQA programs; UKNEQAS and AQUAS. One hundred and eight laboratories, including 4 laboratories that participate in EQA, intend to join our NEQAS. Nearly all (100) of them could afford the membership fee of 2,000 baht (approximately 50 US dollar) per year.

Table 2. The brand name of PT and APTT reagents or the manufacturer's name (given by some respondents) and of instruments used in the laboratories

(a) PT reagents

Brand name of reagent or manufacturer's name (m)	No of lab (%)
Bio Merieux (m)	3 (2.7)
Diamed Diaplastin	5 (4.5)
Griffols Diagnostic (m)	5 (4.5)
Hemosil	2 (1.8)
PT/FIB Recombinant	3 (2.7)
Simplastin Excel-s	8 (7.1)
Thromborels	71 (63.4)
PT/FIB Recombinant and Thromborels	1 (0.9)
Others (used by one lab each)	9 (8.0)
No answer or not clearly stated	5 (4.5)
Total	112 (100)

(b) APTT reagents

Brand name of reagent or manufacturer's name (m)	No of lab (%)
ActinFS	66 (60.0)
APTT-SP	2 (1.8)
Bio Merieux (m)	4 (3.6)
CK-prest	2 (1.8)
Griffols Diagnostic	5 (4.5)
Diamed Diacelin	4 (3.6)
Hemosil	2 (1.8)
PathromtinSL	3 (2.7)
Platelin	2 (1.8)
Platelin LS	6 (5.5)
Others (used by one lab each)	2 (1.8)
No answer or not clearly stated	12 (10.9)
Total	110 (100)

(c) Instruments

Name of instrument	No of lab (%)
Manual method	3 (2.7)
ACL series	2 (1.8)
Behring Coagulation Timer	2 (1.8)
CA1500	3 (2.7)
CA50	18 (16.1)
CA500 series	19 (17.0)
Fibrintimer	3 (2.7)
Option series	3 (2.7)
ST2, ST4	3 (2.7)
Thrombotimer	4 (3.6)
CA500,CA1500	2 (1.8)
CA-1500,CA500,fibrin timer	1 (0.9)
Others (used by one lab each)	6 (5.4)
No answer	43 (38.4)
Total	112 (100)

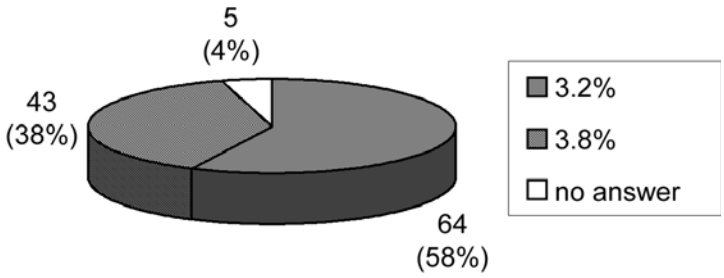
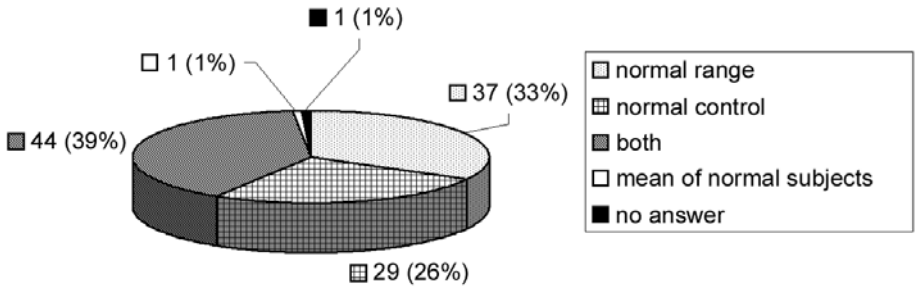
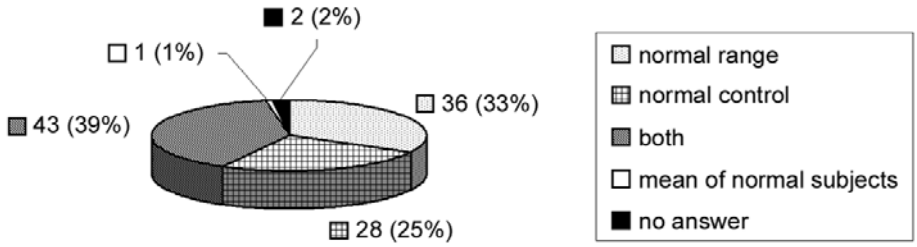


Fig. 1 Number of laboratories that use 3.2% or 3.8% sodium citrate as anticoagulant for blood coagulation tests (n = 112)



(a) PT (n = 112)



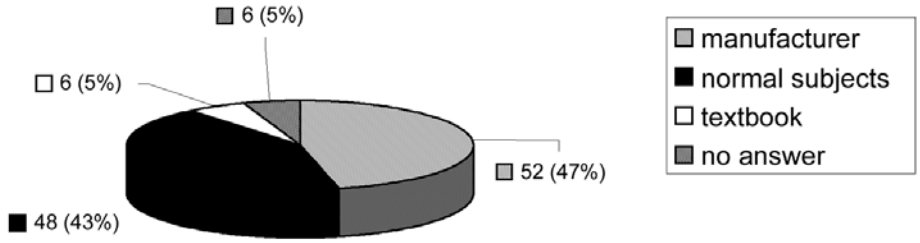
(b) APTT (n = 110)

Fig. 2 The reporting systems of laboratories for PT (a), and APTT (b): the patient's result is reported with normal range, or normal control, or both of them, or mean of normal subjects, the percentage of laboratories is shown in bracket

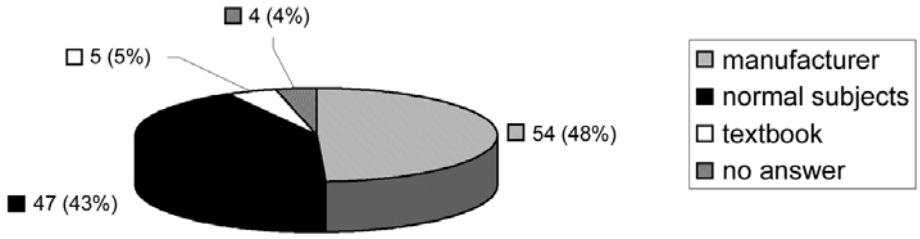
Discussion

The response rate of this survey for coagulation tests of 56.4% was acceptably high compared to a survey of APTT reporting in Canadian medical laboratories which was 50.7% (329 from 649 laboratories)[5]. One possible reason for the number of non-responders was that there was no coagulation laboratory in particular hospitals, and to the authors' surprise, some medium-size hospitals sent back the questionnaires indicating that coagulation tests were not performed. Among the responders, a few laboratories unfortunately did not perform APTT. It is the authors' view that it should be the national policy that hospitals of a certain size should have ability to provide coagulation tests for the patient management.

Regarding the preanalytical phase, in spite of the fact that the use of 3.2% (109 mmol/L) of trisodium citrate as anticoagulant for blood collection is strongly recommended[4,6] 38% of the responding laboratories still use 3.8% (129 mmol/L). The lower concentration of citrate allows more underfilling volume and the results are less affected by samples from the patients with high hematocrits, thus minimizing spurious results caused by overcitrated specimens[7]. Furthermore, 3.2%

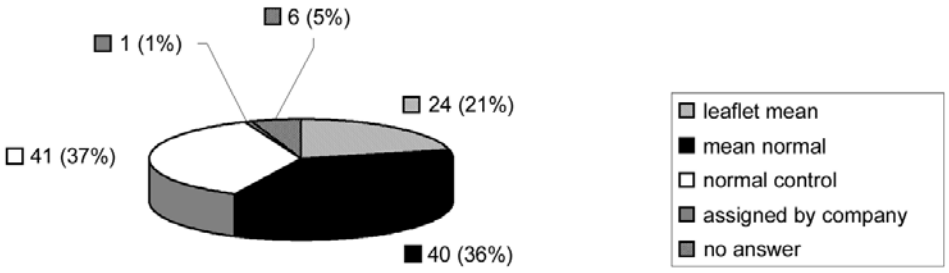


(a) PT (n = 112)

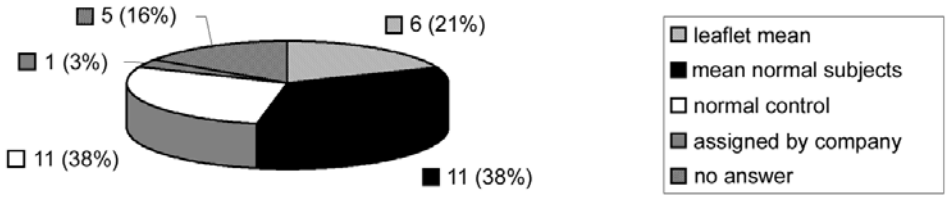


(b) APTT (n = 110)

Fig. 3 The sources of reference range for PT (a), and APTT (b): laboratories derive reference ranges either from the manufacturer's instructions or from a textbook or establish their own using normal subjects, the percentage of laboratories is shown in bracket



(a) PT ratio (for INR calculation)



(b) APTT ratio

Fig. 4 The sources of denominators used for the calculation of PT ratio and consequent INR (a) and APTT ratio (b), laboratories use either mean of reference range from the manufacturer's instructions (leaflet mean) or mean normal subjects (mean normal) or normal control value or assigned by specialist from the company (assigned by company), the percentage of laboratories is shown in bracket

sodium citrate is the concentration used for calibration of reagent ISIs[8].

There are various types of PT, APTT reagents and instruments in Thailand. Nevertheless, the products from one manufacture predominate and this predominance can lead to problems for smaller groups in comparison of test results. WHO IEQAS evaluates performance by comparing the individual participant's results with the median value for the reagent group to which they belong. In the groups of fewer than 10 members, the target median values are not reliable[9], so their performances are compared to the all-method (overall) median[10], which are less useful. However, it is still important to join in an EQA program. The improvement of precision of the PT results indicated by the reduction of the coefficient of variation was recently demonstrated in a small country, which had only nine laboratory members in its scheme[11].

Nowadays, very few laboratories use a manual method, in contrast to the previous national survey done by Talalak P in 1979[12]. While manufactures tend to prepare and calibrate PT reagent to assign ISI (International Sensitivity Index) value merely for automated analyzers[13], this increases the difficulty for those laboratories that use the manual method to report INR correctly.

Laboratories should determine their own reference ranges by using fresh plasma samples from at least 20-30 apparently healthy volunteers. The geometric mean of normal prothrombin time (MNPT) should be subsequently calculated and used for INR determinations. The mid point of APTT reference range is used as a denominator to calculate the APTT ratio[13]. For the UKNEQAS, which is responsible for WHO IEQAS, only the results from laboratories that determine their own reference ranges are included in the calculation of group median values. The performance is evaluated by comparing the participant's result with the median value[14]. According to the survey, most coagulation laboratories do not establish their own reference range. The denominators of INR and APTT ratio calculations are derived from several sources apart from the mean of normal subjects, such as value of normal control plasma. Although there has been a study that substituted the normal value from a lyophilized 'normal' control plasma for MNPT in prothrombin ratio calculation and obtained no significant difference, its results applied only to the specific commercial normal plasma used in that study. To use control plasma from other companies for this purpose, the reliability should be validated[15].

In the aspect of anticoagulant monitoring, PT reported as an INR is now widely practiced for oral anticoagulant control. However, for the monitoring of unfractionated heparin, most laboratories do not establish their own therapeutic range, which is now the standard practice due to the differences in heparin responsiveness of APTT reagents and variation caused by reagent-instrument combination[16,17]. According to the telephone interviews, the laboratories do not recognize the importance of monitoring heparin therapy and there is a lack of communication between the laboratories and clinicians in respect of this.

In the WHO IEQAS, participants are additionally requested to interpret the result of the EQA sample for anticoagulant monitoring as to whether it is adequate, inadequate or over dosage[10]. The authors' NEQAS has to omit this practice since most of the laboratories do not have a therapeutic range.

With regard to post analytical phase, most of the laboratories report patient results together with the normal control value obtained through internal quality control on the same day. This is the old practice, which is currently not recommended. The College of American Pathology (CAP) states clearly in the CAP checklist that the patient results must be reported together with the reference range but without reference to the normal control value, which can cause confusion to clinicians[18].

A small number of laboratories in Thailand participate in an EQA scheme. Since the international EQA schemes have limited accessibility or are costly, most of the respondents were willing to join the authors' NEQAS. After notifying WHO IEQAS that the authors would like to set up NEQAS for blood coagulation, and receiving permission, the first preliminary trial survey was distributed in July 2005, followed by the second trial survey in December 2005. The first formal survey began in 2006 with quarterly sample distributions. Information relating to the establishment of reference ranges and denominators, the recommended range of ISI, and the appropriate anticoagulant concentration were added into the surveys.

In summary, this survey represents an overview of the current laboratory practice for coagulation tests in Thailand, which need to be improved by education, and emphasizes the need for establishing an EQA program in Thailand.

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การสำรวจการปฏิบัติในห้องปฏิบัติการตรวจการแข็งตัวของเลือดในประเทศไทย: ขั้นตอนแรกเพื่อการจัดทำการประเมินคุณภาพจากภายนอกของการตรวจการแข็งตัวของเลือดในระดับประเทศ

พนัสยา เธียรธาดากุล, นิศารัตน์ โอภาสเกียรติกุล, วนิดา วงศ์ถิรพร

ภูมิหลัง: *การประเมินคุณภาพจากภายนอกเป็นส่วนสำคัญของระบบประกันคุณภาพของห้องปฏิบัติการ แต่ในประเทศไทยยังไม่มีระบบการประเมินคุณภาพจากภายนอกของการตรวจการแข็งตัวของเลือดในระดับประเทศ*

วัตถุประสงค์: *เพื่อศึกษารวบรวมข้อมูล ซึ่งเป็นขั้นตอนแรกในการจะจัดตั้งโครงการประเมินคุณภาพจากภายนอกดังกล่าว และเพื่อที่จะทราบวิธีปฏิบัติในห้องปฏิบัติการตรวจการแข็งตัวของเลือดในประเทศไทย*

วัสดุและวิธีการ: *ส่งแบบสอบถามไปยังโรงพยาบาลเพื่อเก็บข้อมูลเกี่ยวกับการปฏิบัติในการตรวจการ แข็งตัวของเลือดและประเมินคุณภาพจากภายนอก*

ผลการศึกษา: *จากแบบสอบถาม 220 ฉบับ ได้รับการตอบกลับ 124 ฉบับ คิดเป็นร้อยละ 56.4 มี 112 โรงพยาบาลที่มีการตรวจการแข็งตัวของเลือด โดยทุกโรงพยาบาลทำการทดสอบ prothrombin time (PT) ส่วน activated partial thromboplastin time (APTT) มีการทำใน 110 โรงพยาบาล ร้อยละ 38 ของห้องปฏิบัติการยังคงใช้ 3.8% โซเดียมซิเตรดเป็นสารกันเลือดแข็งในการเก็บสิ่งส่งตรวจ ร้อยละ 65 ของห้องปฏิบัติการ รายงานค่า normal control ร่วมกับผลการตรวจของผู้ป่วย มีเพียงร้อยละ 42 ที่หาค่าอ้างอิงของห้องปฏิบัติการเอง และมีการใช้ตัวหารในการคำนวณ PT ratio และ APTT ratio ที่ได้จากแหล่งอื่น ไม่ได้ใช้การหาค่าเฉลี่ยในคนปกติตามมาตรฐานสากล มีเพียง 7 ห้องปฏิบัติการ (ร้อยละ 6) ที่ได้เข้าร่วมในการประเมินคุณภาพจากภายนอก*

สรุป: *การสำรวจนี้แสดงให้เห็นถึงการปฏิบัติในการตรวจการแข็งตัวของเลือดในประเทศไทยที่ควรได้รับการปรับปรุงและมีความจำเป็นในการจัดทำโครงการการประเมินคุณภาพจากภายนอกของการตรวจการแข็งตัวของเลือดในระดับประเทศv*