Accuracy of International Normalized Ratio Determined by Portable Venous-Blood Coagulation Monitor *versus* a Central Laboratory

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Abstract

Background : The CoaguChek is a portable monitor unit for measuring the international normalized ratio (INR). The purpose of the study was to evaluate the accuracy of a portable prothrombin time (PT) monitor (CoaguChek, Roche Diagnostics, Mannheim, Germany) compared with the laboratory method.

Material and Method : Paired venous blood INRs were performed in 220 consecutive outpatient tests mainly in anticoagulated (n = 210) and non-anticoagulated (n = 10) individuals. Accuracy was evaluated in 220 tests by parallel assessment of INRs (CoaquChek and laboratory). Accuracy was determined using statistic regression analysis and clinical agreement (expanded and narrow criteria). Agreement in dual INR measurement also was evaluated as a function of increasing INR.

Results : The CoaguChek significantly correlated with the laboratory measurement (r = 0.89). The proportion of dual INR measurements that satisfied the clinical relevant expanded, and narrow agreement criteria was 90 per cent and 86 per cent respectively. Eighty-two per cent of all dual measurements were within 0.5 INR units. The accuracy of the portable monitor was greatest for INR values less than 3.0; above this INR level the portable monitor overestimated laboratory INR values.

Conclusions : The CoaguChek is an accurate alternative to laboratory assessment of INR at values < 3.0. The authors suggest the use of the monitor in non anticoagulated patients or anticoagulated patients at values less than 3, as most physicians in Thailand prefer lower INR than in Western countries.

Key word : Accuracy, Clinical Agreement, Portable INR, Laboratory INR, Warfarin

SIRITHUNYANONT C, BHURIPANYO K, KANGKAGATE C, WINYARAT W, SRICHAYA P, WANGTIP K
J Med Assoc Thai 2003; 86 (Suppl 1): S67-S75

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Oral anticogulant therapy with warfarin is effective antithrombotic treatment for several indications, namely deep venous thrombosis, pulmonary embolism, mechanical heart valves, embolic stroke as well as atrial fibrillation[1]. Patients receiving this therapy are carefully monitored in order to maintain the intensity of anticoagulation in the appropriate therapeutic range[2]. Because warfarin compounds have complex phamacokinetic and pharmacodynamic properties and are among the most challenging drugs to regulate, coordinated anticoagulation clinics may be the preferred means to provide safe and effective care[3]. The results of prothrombin time monitoring should be reported as the international normalized ratio (INR). An INR of 2 to 3 is the recommended therapeutic range for all indications except for the prevention of systemic embolism in patients with mechanical heart valves and for the long-term treatment of patients with myocardial infarction, for whom an INR range of 2.5 to 3.5 is recommended[4-6].

The current preferred method of monitoring warfarin therapy is by monitoring the international normalized ratio (INR) through the traditional laboratory method which requires venipuncture, a costly and time-consuming procedure[7]. At the outpatients Heart clinic in the Bangkok Hospital, patients often spend 1-2 hours waiting for the test results. This can discourage patients from complying with frequent follow-up appointments.

The availability of a portable monitor unit that uses a drop of whole blood obtained by finger stick to determine the INR and prothrombin time (PT) has brought about the possibility of using it as a substitute[8,9]. Accumulating data showed a 50 per cent reduction in the rate of thromboembolism, major hemorrhage, and emergency medical visits with the use of the strategy of anticoagulation clinics ; the use of portable, point of care coagulation monitors, by allowing frequent testing, may further improve outcomes[10]. The aim of this study was to evaluate the accuracy of the portable coagulometer CoaguChek (Roche diagnostics) as an INR monitor, comparisons were done with the criterion standard method of central laboratory of INR determination.

MATERIAL AND METHOD

In the heart clinic of Bangkok Heart Institute, Bangkok Hospital INR is monitored everyday by cardiologists on outpatients. This was a prospective self-controlled study carried out from July to October 2002.

Patients

Patients who received oral anticoagulation therapy for a variety of thromboembolic conditions or mechanical heart valve were consecutively enrolled into the study based on their INR value performed using the hospital's outpatient laboratory equipment. All eligible patients participating in this study provided informed consent.

Study protocol

All patients underwent blood testing during the heart clinic visit to determine the INR using two methods.

Central laboratory method (reference standard)

For all patients venous blood was drawn to completely fill 3 ml of a 3.2 per cent sodium citrate plasma tube; the blood was centrifuged for 10 minutes at 3,500 rpm to obtain platelet - poor plasma. After check in of the specimen, the INR was determined using an analyzer by Sysmex CA-500 with Behring Thromborel S thromboplastin reagent (lot 505577 with an International Sensitivity Index (ISI) of 0.98 ; Behring, Marburg, Germany)

Portable INR monitor method

The CoaguChek INR monitor (Roche Diagnostics, Indianapolis, IN), is a portable laser coagulometer using reflectance photometry that measures the INR using capillary or venous whole blood. The PT^N test is initiated by inserting a CoaguChek pro PT^N test cartridge into the instrument. The instrument reads a code on the test cartridge to determine the identify and lot number. The test cartridge contains a sample application well, reagent chamber, and reaction path. After the instrument has brought the test cartridge to the required temperature, a drop of fresh whole blood is placed on the test cartridge sample application well. The blood is drawn into the reagent chamber by capillary action, where it mixes with the reagent to initiate coagulation. The blood sample moves along the reaction path until a clot forms. The laser optical system detects the clot by monitoring blood flow. The endpoint is reached when the blood clots. The time from sample application to clot detection is the prothrombin time. The calibration at the PT^N test is traceable to the manual tilt-tube method using the International World Health Organization (WHO) reference preparation CRM 149S. Since each newly manufactured lot is matched to an internal reference lot,

any lot-to-lot variability between reagents is corrected electronically using information coded on the lot-specific code key.

Each foil pouch contains one ready-to-use CoaguChek pro PT^N test cartridge for a single determination. Each CoaguChek Pro PT^N test cartridge contains thromboplastin extract from 0.64 mg rabbit brain, antioxidant (0.2 μ g), bacteriostatics (1.9 μ g).

The normal CoaguChek Pro PT^N test is defined as 12 seconds and the ISI for the system is defined as 2.0 seconds. The CoaguChek Pro system displays PT^N results of less than 10 seconds greater than 38 seconds as < 10 seconds or > 38 seconds (< 0.7 INR or > 10.0 INR). The ISI of the reference lot was confirmed to be 2.0 by comparison to the WHO International Reference Preparation CRM149S at five different sites. This ISI value is encoded in the test code together with the Mean Normal Prothrombin Time (MNPT) of12.00 seconds and used to convert the prothrombin time to INR. An INR result is provided within 3 minutes after application of the blood sample to the CoaguChek monitor. In-terms of precision of INR measurements with the CoaguChek monitor, the median coefficient of variation is 5.49 per cent, 8.79 per cent (SD = 0.05, 0.09 INR) for normal capillary, venous blood INR values respectively and 11.39 per cent, 7.34 per cent (SD = 0.34, 0.22 INR) for abnormal INR values of capillary, venous blood respectively.

In the present study simultaneous venous blood samples were used for comparison.

Statistical analysis

Statistical agreement

For all dual INR measurements (portable monitor and central laboratory), the portable monitor INR was plotted as a function of the laboratory INR. Regression analysis by ANOVA was performed and compared against an index of perfect agreement[11].

Clinically relevant agreement

For each dual INR measurement agreement between results from the portable monitor and the laboratory methods was defined using criteria that were considered to be clinically relevant and were modeled on those developed by Douketis et al[12]. Clinically relevant agreement was defined based on whether or not the difference between dual INR measurements would be likely to result in changing warfarin dosage with each INR result. A priori, two categories of clinically relevant agreement were determined:

1) Expanded agreement : when both INR measurements are within the therapeutic range, when both are above the therapeutic range, when both are below the therapeutic range or when one is within the therapeutic range and the pair is within 0.5 INR units. For example for a targeted INR of 2.0 to 3.0 an INR at 2.7 by the laboratory method corresponding to an INR of 3.1 by the portable monitor would not result in a change in the warfarin dose and therefore these two values are considered to be in agreement and 2) Narrow agreement : when both INR measurements are within the therapeutic range or when both are above the therapeutic range and these pairs are within 0.8 INR units, or when both are below the therapeutic range and these pairs and within 0.4 INR units, or when one is within the therapeutic range and this pair is within 0.5 INR units. A wider INR range was used for agreement if both INR values were above the therapeutic range because INR values at 4.3 and 5.0 are likely to result in the sample clinical management whereas for INR pairs that are below the therapeutic range the same difference in INR values at 0.7 units (i.e, 1.2 and 1.9) is likely to result in a different clinical management for each INR result. The proportions of dual INR measurements that satisfied the expanded and narrow agreement criteria were determined using Mc Nemar's test for paired proportions, with 95 per cent confidence intervals for all proportions.

Agreement in relation to magnitude of INR

To investigate the accuracy of the portable monitor compared with the laboratory method as a function of an increasing INR, the difference in INR from each dual measurement (portable monitor INR, laboratory t0, 2.0-3.0, 3.1-4.0 > 4.0.

RESULTS

Patients

The clinical characteristics of the patient populations evaluated in this study are listed in Table 1.

One hundred seventy patients (220 INR tests) agreed to participate and were enrolled into the study. Some patients were tested in a different situation with a different adjusted dosage of warfarin. In the

Table 1. Clinical characteristics of study patients.

	N	%
Patients (n)	170	
INR tests (n)	220	
Age (mean + SD, year)	61.02 ± 14.13	
Gender : men	21	55
INR goal 2.0-3.5	81	36.8
Indication	**N**	**%**
Atrial fibrillation	73	33
Venous thromboembolism	12	5.5
Mechanical heart value (s)	125	56.8
Other (pre-operative evaluation, baseline before starting warfarin)	10	4.5

Heart Clinic, Bangkok Heart Institute the main indication for warfarinization is mechanical heart valve which is mostly the St. Jude valve and some patients had both mitral valve replacement and aortic valve replacement. For most patients with chronic atrial fibrillation or venous thromboembolism or aortic valve prosthesis, the targeted INR was 2.0-3.0; except for 50 patients with mitral valve prosthesis or double valve replacement, the targeted INR was 2.5-3.5.

Comparison of INR measurements with the portable monitor and laboratory methods

Statistical agreement

For all dual INR measurements the relationship between the laboratory INR (x-axis) and the portable monitor INR (-axis) was expressed by regression equation Y = 1.15 X -0.07 (r = 0.89, R square = 0.79) (Fig. 1). The slope and y-axis intercepts values indicated that the portable monitor overestimated the laboratory INR. 82.3 per cent were within 0.5 INR units.

Clinically relevant agreement

For all tests the proportion (and 95% confidence interval) of dual INR measurements that satisfied the expanded and narrow agreement criteria was 89.9 per cent (84.8-92.9) and 85.9 per cent (80.7-89.9), respectively.

Agreement in relation to level of INR

In the analysis of the difference in each dual INR measurement (portable monitor INR-laboratory INR) as a function at an increasing INR there was increased scatter for INR values above 3.0 indicating that the portable monitor over estimated the laboratory INR values that were in the supratherapeutic range for most patients who were receiving warfarin (Fig. 2).

The mean difference between portable INR-laboratory INR was 0.23 ± 0.57 ($p < 0.001$), when categorized in INR values for laboratory INR ranges of < 2.0, 2.0-3.0, 3.1-4.0 and > 4.0 was 0.18, 0.21, 0.44, 1.38 INR units, respectively. The proportion of dual INR measurements within 0.5 INR units for laboratory INR ranges of < 2.0, 20.-3.0, 3.1-4.0 and > 4.0 was 94 per cent, 83 per cent, 50 per cent, and 40 per cent respectively (Table 2).

Most Thai patients were anticoagulated with low INR (INR < 2.0, = 119 patients; 2.0-3.0 = 76 patients). There were 10 non-anticoagulated patients.

DISCUSSION

In the present study the authors demonstrated that the CoaguCheck rapid-response device was shown to be highly correlated with laboratory INR values (r = 0.89) and agreement in therapeutic decisions or agreement in dosage alteration was found in 86-90 per cent of the time. Based on the present analysis, the authors concluded that the CoaguChek monitor achieved a clinically acceptable level of accuracy. Accuracy was best at INR < 3. Above this level the CoaguChek monitor tended to overestimate the INR. This is of concern in the risk of thrombosis, especially patients who have heart valve replacement. Alternatively, the regression analysis equation may be used to predict the actual INR value of the lab test when known the portable INR value is known or it may be repeated in the central lab for comparison. So the purpose of further study is to study the sensi-

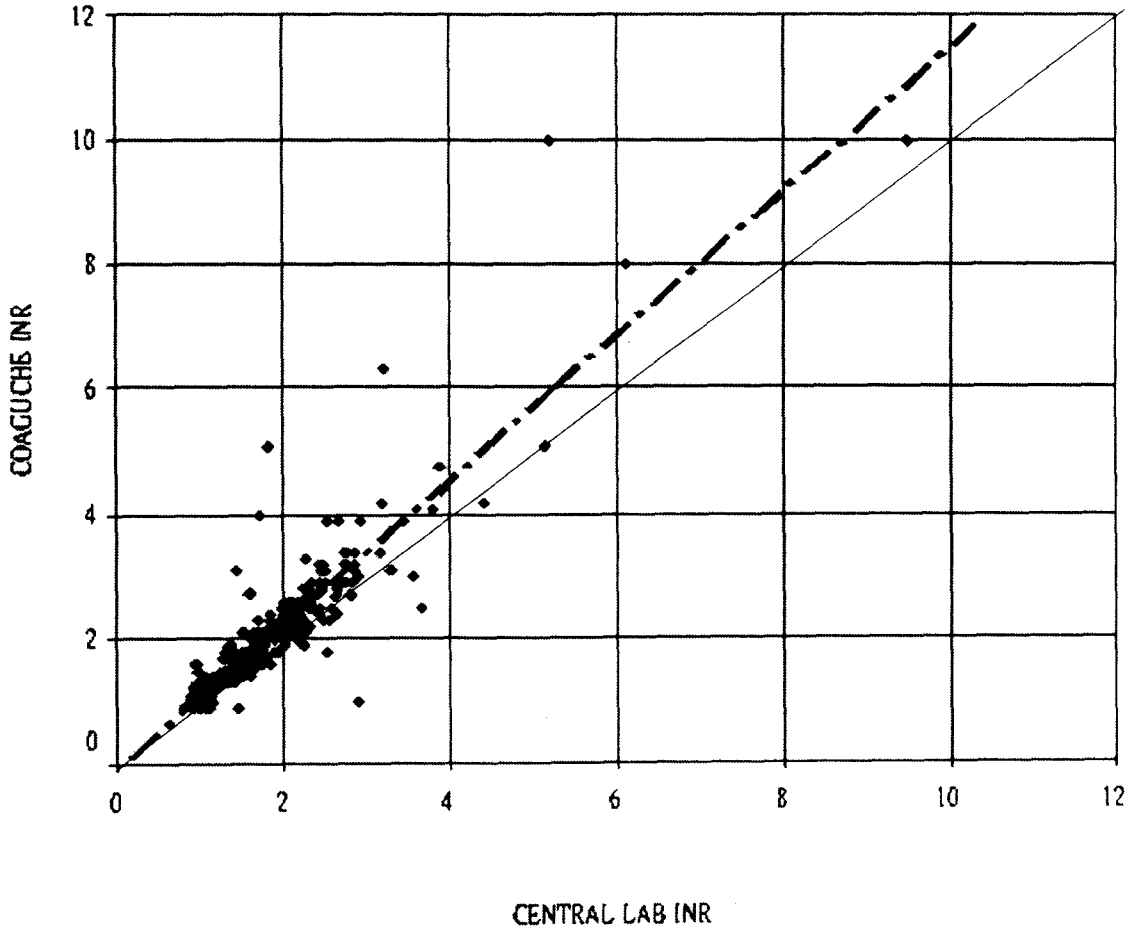

Fig. 1. Scattergram showing relationship between CoaguChek INR and central laboratory INR.

tivity and specificity of regression analysis equation in large groups of patients.

In a study by Cosmi et al[13], Reed and Rickman[14] showed an overestimation of INR values above 3. In contrast, the study by Douketis et al[12], Wong et al[15] showed that for INR > 3, the CoaguChek monitor consistently underestimated the INR when compared with the laboratory method. Other portable monitors showed a similar trend[16-18].

In the present study it is reassuring that the portable monitor was very accurate for INR results less than 3.0 the mean difference between portable INR results and laboratory INR results for this INR range was about 0.2 INR units. However, for laboratory INR value greater than 3.0 a mean difference between the portable and laboratory methods was between 0.44 and 1.38 units. A wider margin of error may be because of the small group of patients or the thromboplastin in the CoaguChek reagent strip is from rabbit brain, whereas that from the laboratories is from human placenta. This could account for the CoaguChek monitor being less or more sensitive to the anticoagulant effects of warfarin[18] with increasing INR.

The INR determination can be improved by using more responsive thromboplastins with ISI, in the range of 1 to 2[19-21]. The different sensitivities of thromboplastin ISI in the present study (central lab ISI = 0.98, protable CoaguChek ISI = 2.0) may lead to different values of converting the PT to INR in patients on anticoagulants and similar thromboplastin reagents or the ISI may have better agreement.

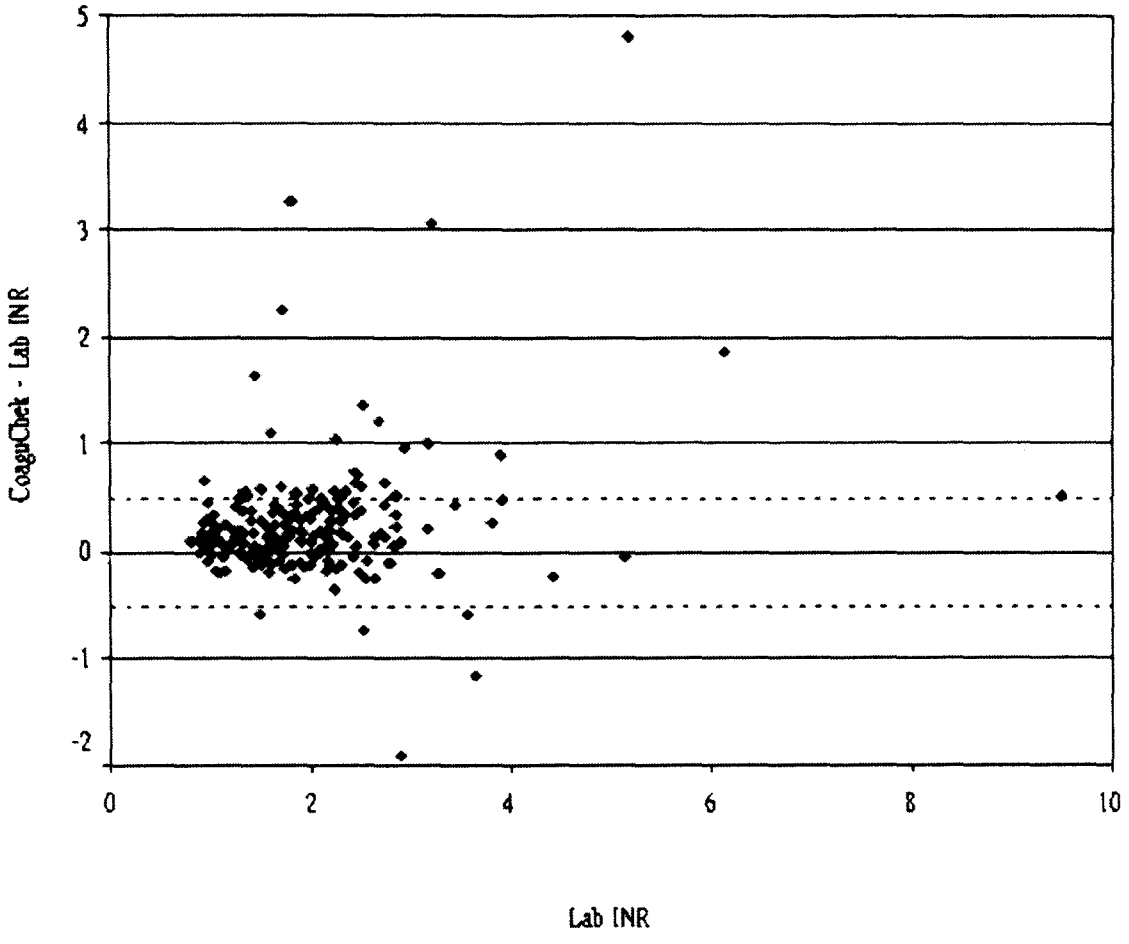

Fig. 2. **Scattergram showing agreement in relation to level of INR (by determining difference in each dual INR measurement).**

Table 2. **Agreement of INR from the central lab and the portable INR as a function of increasing INR for all tests (n = 220).**

INR range (central lab)	N	Dual measurement	
		Mean difference (INR units)	% within in 0.5 INR units
< 2.0	129	0.18	97.8
2.0-3.0	76	0.21	82.9
3.1-4.0	10	0.44	50
> 4.0	5	1.38	4

The next-generation device, CoaguChek -S is a clinical laboratory improvement amendment-waived, point-of care coagulant device found to have comparable accuracy and precision to that of the older monitor system (CoaguChek) with fewer technical errors and agreed with the laboratory at INR values < 4.0 with precise results[22]. In most Thai patients who are receiving warfarin, INR values greater than 4.0 are likely to result in temporarily holding with warfarin or a dose reduction. In the present study,

when we reviewed 5 patients with INR values > 4 both portable and laboratory INR value, the drug were withheld and one patient had hemorrhagic pericardial effusion and needed intervention to treatment.

When compaing the cost in Bangkok Hospital, the portable INR cost was 140 baht, the central lab INR cost was 350 baht and took at least 1 hour to interpret the result, while the portable INR took only 3 minutes.

SUMMARY

The present study demonstrates that the CoaguChek portable INR monitor has the potential to improve the management of patients receiving long-term warfarin by reducing patient inconvenience related to laboratory-based INR measurement, increasing patient compliance with INR monitoring and facilitating more frequent INR monitoring. However, it needs to be used with caution in patients with INR > 3. As with prior evaluations of point-of-care monitors and laboratories, as the INR increased, the accuracy and precision were reduced. So, with any method of measuring the INR, if a high value is found that is not consistent with what was expected, a repeat test using an alternative method may be considered.

Randomized controlled trials should be performed to determine whether these advantages are cost-effective and result in a decrease in the incidence of bleeding and thromboembolic events.

ACKNOWLEDGEMENT

The authors wish to thank Roche Diagnostics (Indianapolis, IN) who provided financial support and supplied monitors and equipment for this study.

(Received for publication on March 10, 2003)

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ความแม่นยำของการตรวจ ไอ เอ็น อาร์ ระหว่างอุปกรณ์ข้างเตียงกับห้องปฏิบัติการ

จีระศักดิ์ สิริธัญญานนท์, พบ, เกียรติชัย ภูริปัญโญ, พบ*, จารุวรรณ คังคุเกตุ, วทบ**, วิราณี วิญญูรัตน์, พยบ*, พนารัตน์ ศรีฉายา, พยบ*, กนกขวัญ วังทิพย์, พยบ**

วัตถุประสงค์ : อุปกรณ์ตรวจการการแข็งตัวของเลือดแบบ ไอ เอ็น อาร์ (INR) โดยใช้อุปกรณ์ข้างเตียงสามารถทำได้สะดวก รวดเร็ว การศึกษานี้เพื่อประเมินความแม่นยำของการตรวจวิธีนี้ เปรียบเทียบกับห้องปฏิบัติการ

ผู้ป่วยและวิธีการศึกษา : ประเมินโดยใช้เลือดตรวจพร้อมกันด้วยอุปกรณ์ข้างเตียงกับส่งทางห้องปฏิบัติการ เพื่อเปรียบเทียบ ความแม่นยำถูกประเมินใน 220 ตัวอย่าง ส่วนใหญ่ตรวจสอบในผู้ป่วยที่กินยาละลายลิ่มเลือด (210 ตัวอย่าง) ความแม่นยำถูกทดสอบ โดยใช้สมการทางสถิติแบบสอดคล้อง และดูความสอดคล้องทางคลินิกร่วมด้วย นอกจากนี้ดูความสัมพันธ์ในลักษณะของการเพิ่มขึ้นของระดับ ไอ เอ็น อาร์

ผลการศึกษา : การตรวจด้วยอุปกรณ์ข้างเตียงมีความสอดคล้องอย่างมีนัยสำคัญทางสถิติกับการตรวจทางห้องปฏิบัติการ ($r = 0.89$) สัดส่วนที่มีความสอดคล้องทางคลินิกตามหลักเกณฑ์แบบเชิงกว้างและเชิงแคบเท่ากับ 90 และ 86% ตามลำดับ 82% ของการตรวจทั้ง 2 แบบอยู่ในช่วง 0.5 ไอ เอ็น อาร์ เดียวกัน ความแม่นยำของอุปกรณ์ข้างเตียงมากที่สุดที่ระดับ ไอ เอ็น อาร์ น้อยกว่า 3 ในระดับ INR ที่สูงขึ้น อุปกรณ์ข้างเตียงมีค่าสูงกว่าทางห้องปฏิบัติการ

สรุป : การตรวจด้วยอุปกรณ์ข้างเตียงมีความแม่นยำพอ ๆ กับทางห้องปฏิบัติการในระดับ ไอ เอ็น อาร์ ที่น้อยกว่า 3 ซึ่งแพทย์ไทยต้องการระดับ ไอ เอ็น อาร์ นี้ในการรักษาผู้ป่วย

คำสำคัญ : ไอ เอ็น อาร์ ระหว่างอุปกรณ์ข้างเตียง, ยาละลายลิ่มเลือด, ไอ เอ็น อาร์ ในห้องปฏิบัติการ

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จดหมายเหตุทางแพทย์ ฯ 2546; 86 (ฉบับพิเศษ 1): S67–S75

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