A Comparative Study of Portable Monitors (CoaguCheck® XS) for International Normalized Ratio (INR) Determination with a Laboratory-Based System for Control of Oral Anticoagulant Treatment

Voraporn Poomlek, M.D.*, Wanut Chaithree, M.D.*, Punnarerk Thongcharoen, M.D.**, Pradit Panchavinnin, M.D.***, Nisarat Opartkiattikul, M.D., Ph.D.*
*Department of Clinical Pathology, **Department of Surgery, ***Department of Internal Medicine, Faculty of Medicine, Siriraj Hospital, Mahidol University, Bangkok 10700, Thailand.

Correspondence to: Nisarat Opartkiattikul
E-mail: sinop@mahidol.ac.th

ABSTRACT

Objective: To evaluate the accuracy and precision of INR determination of CoaguCheck® XS compared to the standard laboratory method among patients with long-term warfarin therapy.

Methods: 39 patients receiving long-term warfarin were eligible in this study. Parallel INR measurements were performed. Capillary INR (INR_C) measurements were determined with CoaguCheck® XS and venous INR (INR_V) were determined with standard laboratory methods.

Results: We found an excellent correlation coefficient ($r^2 = 0.968, 95\%CI = 0.82 - 0.99$) between INR_V and INR_C among 39 patients receiving long-term warfarin. The mean difference between the two methods was 0.16 ($p<0.0001$). Although these differences were statistically significant, they were not clinically significant. In 97.4% of the INR parallel measurements the differences between the two methods were within 0.5 INR units. The Bland-Altman difference plot showed greater variation with increasing mean INR values. The coefficient of variation of CoaguCheck® XS was 1.07%.

Conclusion: The CoaguCheck® XS was comparable in accuracy to a standard laboratory method. Its precision was good. It might be a suitable alternative to monitor INR values among patients receiving oral anticoagulants by increasing patient compliance with INR monitoring, and facilitating more frequent INR monitoring especially in highly educated patients.

Keywords: Anticoagulant therapy; CoaguCheck® XS; INR; warfarin

Siriraj Med J 2008; 60: 10-13
E-journal: http://www.sirirajmedj.com

Demands for warfarin have greatly increased in recent years.1 Long time oral anticoagulant therapy with warfarin is recommended for patients with chronic atrial fibrillation, venous thromboembolism, valvular heart disease, or a mechanical prosthetic heart valve.2 In patients receiving warfarin, measurement of the Prothrombin Time (PT) / International Normalization Ratio (INR) should be performed every 1-2 months to monitor the level of anticoagulation, because the dose-response of warfarin can vary and is influenced by changes in concomitant drug use, dietary habits, and alcohol consumption.2 Frequent monitoring and dose adjustment of the anticoagulant therapy are necessary to maintain the intensity of anticoagulation at a level capable of preventing thromboembolic complications without increasing the risk of minor or major bleeding.2,3

The increase in the demand for oral anticoagulants has led to the search for a new system of control that will improve patient’s quality of life, involving self testing compatible with ensured levels of therapeutic effectiveness. The new portable systems consist of small monitors that utilize capillary whole blood for PT/INR determination, avoiding some of the preanalytical errors introduced by standard laboratory method.4,5 In addition, a reasonable time for standard routine daily service coagulation tests...
are 4 hours.14,15 However, the INR results performed with the standard laboratory method of the Department of Clinical Pathology, Siriraj Hospital are available within 1-1.5 hours, whereas the portable INR monitors provide results within 5 minutes. This leads to the potential to allow health care providers to assess the anticoagulant status of patients who are receiving warfarin therapy.

To date, several studies have supported the reliability between portable INR monitors and a standard laboratory INR method16. However, in Thailand, the portable INR monitors have scarcely been used, and there have been insufficient studies to support their use.

The purpose of this study was to compare INR values in a group of long-term anticoagulated patients. Determined on the portable INR monitor (CoaguCheck® XS), using capillary whole blood, with INR values measured in a venous plasma sample with the standard method of the Department of Clinical Pathology Siriraj Hospital. This is the only one of its kind in Thailand that is a member of the WHO International External Quality Assessment Scheme in Blood Coagulation and the external quality assurance of PT/INR results have always been classified as “within consensus”16.

MATERIALS AND METHODS

Patients
39 consecutive ambulatory patients who had been receiving long-term anticoagulant treatment for at least 6 weeks, and who had been monitored by the Cardiovascular-Thoracic (CVT) clinics of Siriraj Hospital, were eligible for this study. The patients participating in this study were both male and female, aged more than 18 years. Patients who discontinued oral anticoagulants within 1 week at the time of visit, or had signs of bleeding, and couldn’t make capillary whole blood collection from any cause, were excluded from this study. This study was approved by the Ethics Committee. All patients provided and signed their informed consent.

Study protocol
All patients underwent blood testing during their visits to the clinic to determine the INR using two methods.

Standard method
For all patients, venous blood was drawn by venipuncture from an antecubital vein into a one-tenth volume 0.105 M (3.2%) sodium citrate vacutainer tube. The plasma was prepared by centrifugation at 3,000 rpm for 15 minutes. All plasma obtained was determined by the CA1500 (Sysmex) (INR_V), using Thromborel®S (human thromboplastin containing calcium) with an international sensitivity index (ISI) = 1.00 supplied by the manufacturer. The mean normal PT was determined by the geometrical mean of 30 fresh normal plasmas.

Portable INR monitor method (CoaguCheck®XS)
The fresh capillary whole blood samples (single drop, approximately 10 μl) were collected with an Accu-chek Softclix® lancet system (Roche Diagnostics) from a finger-tip puncture. These samples were directly applied to the sample application area of the CoaguCheck® XS disposable test strip (lot.no.20148433). The test strip is inserted into the meter and prewarmed to 37°C. The capillary blood applied to the application field comes into contact with the thromboplastin, triggering the coagulation cascade leading to the formation of thrombin. The enzyme thrombin cleaves Electroxyyme TH, into a residual peptide and electrochemically active phenylenediamine thereby generating an electrical signal. The time lapse from addition of sample to signal generation is used to calculate the INR value (INR_C).17

Statistical analysis
The data were presented as mean, standard deviation (SD) and percentage, where appropriate. The correlation between the INR_C and the INR_V were determined using the Pearson’s correlation coefficient test. A paired t-test (p<0.05 considered significant) was used to compare the INR values between the INR_C and the INR_V. Regression analysis of the data was performed with the Passing Bablock method. Confidence intervals (CI) were calculated at the 95% level. A Bland-Altman plot was performed to assess the magnitude of disagreement between the two INR results.15 In addition, the respective INR ranges of all dual measurements within 0.5 INR units were determined. In terms of precision of INR measurement with the CoaguCheck® XS, the percentage of coefficient of variation (CV) was calculated. The CV was assessed by 35 repeated CoaguCheck® XS control samples with therapeutic INR values (2-3 INR units).

RESULTS

Patient characteristics
Dual INR measurements using the portable CoaguCheck® XS and standard methods were determined in 39 patients who were receiving long-term warfarin. In 48.7% and 43.6% of the patients measured as INR_V and INR_C respectively, the INR values were between 2-3. In 35.9% and 41% respectively, the INR values were below 2.0. In 15.4% and 15.4%, respectively, the INR values were above 3.0 (Table 1).

Comparative INR between CoaguCheck® XS and standard laboratory methods
The CoaguCheck® XS INR values were significantly correlated with the standard INR values (r² = 0.968, 95%CI = 0.82 - 0.99, p < 0.001; Fig 1). For all dual INR measurements, the relationship between the values of the standard laboratory INR method (INR_V) and the CoaguCheck® XS INR method (INR_C) was expressed by the regression equation : INR_C = 1.01(INR_V) - 0.19 (Fig 1).

The mean difference of the INR (standard minus CoaguCheck® XS) was 0.16 (95%CI: 0.11 - 0.21; paired t = 6.7, df = 38, p < 0.0001). The mean difference of dual INR measurement within 0.5 INR units for INR values with ranges of <2, 2-3,>3 are shown in Table 2. In 97.4% (38 of the total 39 patients) the difference between the INR_V and INR_C was not higher than 0.5 INR units. Only 1 case in the range of INR 2 - 3 was the difference 0.57 (Table 3).

The coefficient of variation (CV) of CoaguCheck® XS was 1.07% for therapeutic INR value (2-3 INR units). The plotting of the average INR value of a pair of measurements versus their difference (the INR_V - INR_C) is shown in Fig 2. The CoaguCheck® XS showed slight variation with the standard method for INR values below 2.5. The different INR values increased with a higher average INR.

TABLE 1. Number of the INR value in the respective INR ranges obtained using the standard laboratory method (INR_V) and CoaguCheck® XS (INR_C)

<table>
<thead>
<tr>
<th>INR value</th>
<th>INR_V</th>
<th>INR_C</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 2</td>
<td>14 (35.9%)</td>
<td>16 (41%)</td>
</tr>
<tr>
<td>2-3</td>
<td>19 (48.7%)</td>
<td>17 (43.6%)</td>
</tr>
<tr>
<td>&gt;3</td>
<td>6 (15.4%)</td>
<td>6 (15.4%)</td>
</tr>
</tbody>
</table>
DISCUSSION

In this study, we evaluated the accuracy and precision of a new, rapid-response, portable INR monitor (CoaguCheck® XS) as compared with the standard laboratory methods to measure the INR in patients receiving long-term warfarin.

The portable CoaguCheck® XS (Roche Diagnostics) is a hand-held, point-of-care device which measures the Prothrombin time (PT) and the International Normalized Ratio (INR) of fresh capillary whole blood applied to disposable test strips. Each strip contains on-board quality control (QC) features to monitor the strip integrity. The CoaguCheck® XS performs an electrochemical measurement of a PT test using a human recombinant tissue factor (hrTF) reagent, also known as thromboplastin (ISI = 1.00) and a peptide substrate Electrocyte TH. Electrocyme TH is used for the determination of serine proteases such as thrombin.12

The master lot of CoaguCheck® XS PT test strips were calibrated against the international reference preparation (rTF/95 and CRM 149S) by the WHO reference method (20 normal and 60 patients INR 1.5-4.5). Further calibration in a production lot of test strips is performed versus this master lot using whole blood samples from 10 normal donors and from 30 patients. Calibration information specific to each lot of test strips is coded in a lot specific chip that is inserted into the monitor. The CoaguCheck® XS could report the INR results in a range 0.8 - 8.0 INR units.

From the result of the comparison between CoaguCheck® XS and standard methods, we found an excellent correlation between the two methods with a coefficient of correlation of 0.968 (95% CI = 0.82 - 0.99, \(p<0.001\)). Similar results have been found by others.6,7,8,9

When comparing the accuracy of a coagulation monitor, the question of which comparator to use is crucial. The true gold standard for the INR value is to test using the manual tilt-tube technique with the use of a World Health Organization IRP thromboplastin.5,11 However, as the comparison to the true gold standard was not available, the reference INR method used in our study was a standard laboratory method. Our standard laboratory method is the only one of its kind in Thailand which is a member of the WHO International External Quality Assessment Scheme in Blood Coagulation and the external quality assurance of PT/INR results have always been classified as ‘within consensus’.10 So we decided to use our system as a gold standard.

We found a mean difference between the INR_V and INR_C of 0.16 (95%CI: 0.11 - 0.21; paired \(t=6.7, df=38, p<0.0001\)). Although these differences were statistically significant, they were not clinically significant and were small in magnitude. We found that 97.4% of all dual measurements were within 0.5 INR units. The CoaguCheck® XS INR values were less than when compared to the standard INR values. In addition, we found a very high precision with a coefficient of variation of 1.07%.

The Bland-Altman difference plot showed a trend to greater deviation from the standard laboratory method when the INR was above 2.5 units. Although, we observed greater deviation from the standard laboratory INR above 2.5 units, the difference between the two methods was mostly within 0.5 INR units. (We found only one value where the difference between the two methods was more than 0.5 INR units). However, this difference had no clinical meaning (INR_V = 2.97, INR_C = 2.4).

CONCLUSION

This study demonstrates that the CoaguCheck® XS was found to have comparable accuracy to a standard
laboratory method and high precision in INR testing. It is a suitable alternative to monitor the INR value among patients receiving oral anticoagulants by increasing patient compliance with INR monitoring, and facilitating more frequent INR monitoring especially in highly educated patients. The ease of use, accuracy and rapid availability of the INR results have the potential to reduce preanalytical errors and adverse events associated with oral anticoagulant therapy.

ACKNOWLEDGEMENTS

The authors wish to thank Mr. Suthipol Udompunturak for his statistical assistance and the whole staff of the Department of Clinical Pathology, Faculty of Medicine Siriraj Hospital, Mahidol University.

REFERENCES