Original Article

Comparison of Prothrombin Time and International Normalized Ratio Values using Point-of-care System with a Standardized Laboratory Method in Patients on Long-term Oral Anticoagulation – A Prospective Study

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Abstract

Background: In our country, methods of prothrombin time (PT) and international normalized ratio (INR) testing have not been standardized across various centers. Often, we find disparity in INR values from different laboratories, posing a challenge to make an appropriate clinical decision. Objective: The objective of the study was to compare and correlate the PT/INR values using a point-of-care (POC) system with standardized laboratory (SL) testing and to evaluate the efficiency of the POC system in monitoring patients. Methods: We have prospectively compared PT/INR values between a commercially available POC, CoaguChek XS System, Roche, and SL testing in 205 patients and 353 samples from July 2017 to April 2018. Results: The overall strong correlation between POC PT/INR values and simultaneous standard laboratory values was noted. The overall coefficient of correlation among the two groups was 0.919 ($P = 0.001$) for INR values. In INR range of 2–3.5, the values correlated well with a coefficient of correlation, 0.756 ($P = 0.001$). In INR range <2, the values correlated with a coefficient of 0.98. The correlation was poor when the INR values were >4. Conclusions: In this comparison study, statistical analysis yielded a good correlation between POC PT/INR values and SL values in therapeutic and subtherapeutic range. POC testing is a good alternative to SL testing. If widely available, POC testing may enable patient self-testing and self-monitoring. In our experience, POC testing had added benefits in emergency settings. However, clinicians and laboratory professionals should be aware of the occasional disagreement between POC INR and standard laboratory INR values.

Keywords: Long-term oral anticoagulation, point-of-care testing, prothrombin time/ international normalized ratio values, standard laboratory testing

Introduction

Physicians worldwide prescribe Vitamin K antagonists (VKA) for chronic anticoagulant therapy for a number of clinical indications. However, numerous patient-specific factors influence warfarin sensitivity. These include age, body mass, nutritional status, hepatic function, and genetic variations in the cytochrome P450 complex and Vitamin K epoxide reductase complex 1.¹ In addition to these patient-specific factors, warfarin has a narrow therapeutic window that requires frequent international normalized ratio (INR) monitoring to minimize hemorrhagic and thromboembolic complications.

Point-of-care (POC) testing of the INR method was developed to standardize prothrombin time (PT) results between different PT analyzers and thromboplastin reagents.³ Over the past two decades, different manufacturers have developed several POC INR devices that use finger-stick samples of the whole blood to measure the clotting time. These instruments then estimate INR using conversion formulas derived by the device manufacturers from the comparison of clotting times to a reference PT assay. Although commercially available,

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these devices are being less commonly utilized for various reasons. We sought out to compare and correlate the PT/INR values using POC system with standardized laboratory (SL) testing and evaluate the efficiency of POC system for PT/INR monitoring in patients on oral anticoagulant therapy.

**Methods**

The study has been conducted at a tertiary care hospital after institutional ethics committee approval. Informed and written consent has been obtained from all of the patients. We tested PT/INR in 205 consecutive patients on oral anticoagulation (OAC) visiting the cardiology outpatient department and 353 samples from July 2017 to April 2018 (over 10-month period) in a prospective manner. A capillary blood sample was tested using the POC CoaguChek XS system, Roche, and a simultaneous venous sample was tested using our SL method which served as a control. In disagreement of POC and SL values, we used laboratory values for clinical decision making. We included consecutive patients on chronic VKA therapy visiting the cardiology OPD at our institute for routine PT/INR monitoring. Patients who were unable to or refused to give consent and critically ill patients were excluded from the study. Patients on novel oral anticoagulants (NOACs) for nonvalvular atrial fibrillation (AF) were also excluded.

Laboratory testing was done using a commercially available HemosILTM system which uses a very high-sensitivity calcium thromboplastin for simultaneous determinations of PT and fibrinogen for evaluation of the extrinsic coagulation pathway and monitoring OAC therapy in human citrated plasma on the IL coagulation systems. This system uses a reagent PT-FiB HS PLUS, which is a lyophilized rabbit brain extract with an optimal concentration of calcium ions.[23] This product is manufactured with high sensitivity to Factors II, V, VII, and X, comparable to international reference preparations making it particularly suitable for monitoring VKA therapy. Our SL system had both internal and external quality controls. The internal quality control was run every day (10 samples before usage) and external quality control periodically (quarterly) from an international reference laboratory (the Christian Medical College, Vellore).

The CoaguChek XS System [Figure 1a and b] is a commercially available third-generation handheld portable monitor used for PT testing.[3,4] The results were provided in PT (in seconds) and INR in units. This POC system is intended for use by health-care professionals to evaluate the PT/INR of individuals using oral VKA therapy. The POC testing and SL testing were done at different sites within the hospital with POC testing done usually in the physician chamber itself. Sampling was done by different groups of health-care professionals who were completely blind to each other’s results. Other important details such as demographic characteristics; indication for OAC therapy; details of underlying heart disease; details of comorbidities such as diabetes, hypertension, smoking habit, dyslipidemia, and history of MI; type and duration of AF; the presence of prosthetic valves; CHA2DS2-VASc score, HAS-BLED score; and medication being used were recorded.

**Statistical methods**

Statistical analysis was done using IBM SPSS Statistics, Version 25.0. Armonk, NY: IBM Corp., and the significance level was set as P <.05 in all statistical analyses. The variables were investigated with the use of analytical methods (Kolmogorov–Smirnov/Shapiro–Wilk tests) to determine whether they were normally distributed. Descriptive statistics were reported as mean with standard deviation for normally distributed continuous variables and as the frequency with percentages for the categorical variables. Various tests used were independent t-test, paired t-test, and Pearson’s correlation test. The correlation between methods was assessed using the Pearson correlation test. Scatter correlation plots were used to depict the agreement of the PT/INR results between CoaguChek XS and HemosIL systems and between various subgroups of the study population. Subset analysis was performed in the following groups (i) between males and females, (ii) age ≤65 and >65 years, (iii) CHA2DS2-VASc score >2 and ≤2, (iv) between patients with nonvalvular AF and valvular AF with or without prosthetic valves, the overall correlation and difference were also compared in three INR ranges (INR <2.0, INR 2–3.5, and INR >3.5), and (v) INR range groups <2, 2–3.5, and >3.5. Pearson correlation coefficient (r) was used for assessing the degree of agreement.
between methods. We considered values of <0.65 as poor correlation, 0.65–0.8 as good correlation, and values >0.8 as excellent correlation for this study purpose.

Results
The study population constituted 96 males (47%) and 109 female patients. The mean age of the population was 57.8 ± 26 years. One hundred forty-three patients (70%) were of age ≤65 years. The remaining 62 patients (30%) were of age ≥66 years. The most common indications for VKA therapy in our study population were pure AF and prosthetic valves with or without AF. The rest of the indications comprised pulmonary thromboembolism, deep-vein thrombosis, severe idiopathic pulmonary arterial hypertension, and severe left ventricular dysfunction Figure 2. Many of the patients underwent sampling more than once during their subsequent outpatient visits. Hence, the total number of samples was 353.

Overall, there was a strong correlation between POC PT and INR values when compared to simultaneous values of the standard laboratory. The coefficient of correlation for INR values was 0.919 with \( P < 0.001 \) and the coefficient of correlation for PT values was 0.941 with \( P < 0.001 \) [Figure 3a and b].

Correlation between males and females
In both male and female patients, the POC PT/INR values correlated strongly with the standard laboratory values with correlation coefficients 0.910 and 0.922, respectively \( (P < 0.001) \). There was no statistically significant difference among both the groups [Figure 4a and b].

Correlation between patients with age ≤65 and ≥66
The correlation was strong in both the age groups ≤65 and ≥65 with \( P < 0.001 \). The correlation coefficients for males and females were 0.902 and 0.916, respectively. There was no significant statistical difference among the two groups [Figure 5a and b].

Correlation between patients with nonvalvular atrial fibrillation and valvular atrial fibrillation with or without prosthetic heart valves
In patients with nonvalvular AF, POC INR correlated significantly with laboratory INR with a coefficient of correlation 0.912 \( (P < 0.001) \). In patients with valvular AF with or without prosthetic heart valves, the POC INR correlated significantly with laboratory INR values with a coefficient of correlation 0.932 \( (P < 0.001) \). There was no significant statistical difference among the two groups [Figure 6a and b].

Correlation between patients with \( \text{CHA}_2\text{DS}_2\text{-VASc} \) score ≤2 and ≥3
In patients with \( \text{CHA}_2\text{DS}_2\text{-VASc} \) score ≤2 and ≥3, POC PT/INR values correlated significantly with laboratory values \( (P < 0.001) \), coefficient of correlation being 0.909 for patients with score ≤2 and 0.915 for patients with score ≥3. There was no significant statistical difference among the two groups [Figure 7a and b].

Correlation in different ranges of international normalized ratio
In patients with INR range of 2–3.5, the values correlated well and the coefficient of correlation was 0.756, with \( P < 0.05 \). In patients with INR <2, the values correlated extremely well with the coefficient of 0.98 with \( P < 0.001 \). The correlation was poor when the INR values were more than 3.5 with a correlation coefficient of 0.65 with a \( P = 0.07 \) [Figure 8a and b].

Figure 2: Pie chart showing various clinical indications for Vitamin K antagonists therapy in the study population

Figure 3: (a) Correlation plot of international normalized ratio values-point of care versus standardized laboratory for the study population. (b) Correlation of prothrombin time values-point of care versus standardized laboratory values for the study population
We did not have any patient samples with INR more than 10 in standard laboratory testing results. Four samples were detected to have INR value >8 in POC testing and showed as “high.” All these four patients had INR values between 8 and 10 in the standard laboratory testing.

**Discussion**

Even with the advent of NOACs and their proven superiority or noninferiority over VKA therapy with respect to clinical efficacy or bleeding complications in most of the clinical scenarios, VKA therapy still may have to be used in many patients, particularly in patients with prosthetic heart valves and valvular AF. Valvular AF is still more common than nonvalvular AF in India, unlike the West, primarily due to the burden of rheumatic heart disease. The higher cost of NOAC agents also limits their usage in India. One of the major disadvantages of VKA therapy is the requirement for periodic anticoagulant monitoring.

The standard test for the monitoring of oral VKA therapy is the plasma-based PT test. POC testing of PT/INR is a relatively new method of anticoagulation monitoring available in India for patients on VKA therapy. It has not been validated in real-world settings in our population, particularly cardiac patients, though several POC machines are commercially available. The disparity in the INR values from different laboratories without proper standardization poses a major challenge in making timely clinical decisions. An easier, reliable, and cost-effective method of INR monitoring is desirable in low-resource settings like in our country. Moreover, rheumatic heart disease in India is still predominantly a disease of younger and lower socioeconomic population, making meticulous INR monitoring in these patients with prosthetic heart valves much more difficult. These patients are also more likely to have poor access to optimal health-care monitoring. This problem is magnified in patients who are either transportation challenged or homebound.

Potential advantages of POC INR testing include rapid turnaround times (usually within seconds) and ease of out-of-hospital testing. These qualities greatly help in the INR monitoring of homebound patients and in those for whom drawing venous blood samples is difficult. Furthermore, POC INR devices enable some patients to self-test and self-manage their warfarin therapy with favorable outcomes.[5] Several anticoagulation management services, mainly in the West, also have reported that POC INR devices improve clinical efficiency and patient comfort and satisfaction compared to traditional venipuncture methods.[6] Despite these benefits, POC INR testing has several disadvantages. Severe anemia or polycythemia (hematocrit below approximately 25% or above about 55%), coadministration of other OAC with warfarin (e.g., low molecular-weight heparin), fibrinogen level, and antiphospholipid inhibitors interfere with the results.

The CoaguChek XS system evaluated in the present study is suited for both health-care professional and patient use. Our study demonstrated a good correlation of the CoaguChek XS system using finger-stick whole blood specimens with an SL plasma test as in several independent studies.[7-12] Lakshmy and Kumar from New Delhi, India, studied PT/INR values in 42 patients and concluded that POC systems are reliable and accurate and can be used by patients for monitoring of OAC therapy.[13] To the best of our knowledge, our study is the
The system we used in our study estimates INR by [19]th ed. Philadelphia: Lippincott Williams & Wilkens; 2014. p. 14-16. However, we recommend validating POC PT/INR with testing gives immediate results and rules out out-of-range in window period, eligible for thrombolytic therapy, POC in a patient with acute ischemic stroke on OAC therapy and decision-making is of utmost importance, like for example, in the physician’s office or clinic, a POC system for allows us to decide whether the patient is in range INR or mechanical methods.

Different ISI values to thromboplastin reagents, the positive bias up to 0.5 INR units in the POC systems and different reagents and instrument combinations have been attributed as the causes for this disagreement in a previous study. [17] Awareness of this disagreement is important for physicians to further confirm the findings and ensure appropriate clinical intervention. Most of the current generation POC INR devices use either an electrochemical sensor or a mechanical method to determine the test endpoint, thereby estimating the INR. [18] The system we used in our study estimates INR by the electrochemical sensor and supposedly more accurate than mechanical methods.

Using controlled and standardized POC measurements could lead to better anticoagulation management and patient outcome. POC testing eliminates variables associated with delayed sample transportation and specimen handling also. In the physician’s office or clinic, a POC system for immediate dosage adjustment and patient counseling is possible, without the delay associated with routine laboratory testing. Furthermore, in some clinical scenarios where rapid decision-making is of utmost importance, like for example, in a patient with acute ischemic stroke on OAC therapy and in window period, eligible for thrombolytic therapy, POC testing gives immediate results and rules out out-of-range INR. However, we recommend validating POC PT/INR with hospitals SL before initiating routine clinical use.

Although direct costs may be higher for POC PT testing, it is cost-effective, if we consider indirect expenses of hospital staff, resource utilization and management of adverse events. Indirect and total costs are better controlled under a comprehensive anticoagulation management program. [19] More frequent patient self-monitoring has been shown to help patients with labile INR and reduce unnecessary dosage adjustments and complications.

**Limitations of the study**

We did not assess time in therapeutic range for our patients, as serial INR data of all the patients were not available, however, that is not the objective of the present study. We also did not look for various conditions interfering with POC PT/INR testing in our study population comprehensively. The upper limit of detection of INR values in the POC system used in our study is eight, and patients with values >8 will be shown as “High.” Fortunately, the number of patients with high INR values in our study population was quite low. Moreover, in these patients, INR values were confirmed with the SL method for clinical decision making. Our study was not powered enough to detect the impact of disagreement between the POC and SL INR values on the clinical outcomes.

**Conclusions**

In this largest comparison study from India, we found a good correlation between POC PT/INR values and SL values. This real-world patient data and various other previous studies findings support the fact that POC PT/INR testing with the currently existing machines is a viable alternative to drawing a venous sample and sending it to the laboratory, in terms of both accuracy and cost-effectiveness. The other greatest advantage of POC testing, we feel, is its ability to give rapid and reliable results in the setting of emergencies and allows us to decide whether the patient is in range INR or to rule out “out-of-range” INR. POC INR testing for chronic anticoagulation monitoring when widely available in the country may enable patient self-testing and self-monitoring. It is also useful in patients with labile INR for frequent out-of-hospital monitoring. However, physicians should be aware that the potential disparity may occur between POC and SL at higher INR values and work toward developing institutional protocols for confirmatory testing. With the wide usage of various POC systems, standardization across different manufacturers and reagents can be anticipated for more accurate results.

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**Conflicts of interest**

There are no conflicts of interest.

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