Comparative Evaluation of International Normalized Ratio (INR) Monitoring Between Point-Of-Care (POC) and Laboratory-Based Testing Methods in Patients Receiving Warfarin Therapy in Sultanah Nur Zahirah Hospital

Nurul Najmi Muhammad[1], Rafidah Abd Razak[1], Fong Chui Wei[1], Siti Rahayu Othman[1], Mahfuzah Ishak[1], Mohd Amirul Arif Yaakub[1], Norsima Nazifah Sidek[2], Liyana Ahamad Fouzi[2]

[1] Hospital Sultanah Nur Zahirah, Terengganu, Ministry of Health Malaysia, [2] Clinical Research Centre, Hospital Sultanah Nur Zahirah, Terengganu, Ministry of Health Malaysia

Abstract

Introduction: Monitoring of patients receiving warfarin therapy is done by monitoring their International Normalised Ratio (INR) value, either by using the point-of-care testing (POC-T) or laboratory method. However, there are greater variations at higher INR value as claimed by POC-T device provider.

Objective: The study aimed to compare the INR results obtained using POC-T and laboratory based method and to determine the cut-off point for high INR values generated by POC-T device that should mandate confirmatory testing with the laboratory method.

Methods: This retrospective cross-sectional study involved patients attending the INR clinic from 1 June 2016 to 30 May 2017 who had their INR values tested by both the POC-T method and laboratory-based method on the same day. Data was analysed using SPSS version 20 with $p<0.05$ was considered statistically significant. The INR results were compared using correlation analysis and Bland-Altman plot.

Results: A total of 118 patients were included in the study with 236 INR values analysed. There was a statistically significant difference between the INR values obtained by the POC-T (3.87, standard deviation (SD) 1.71) and laboratory-based method (2.88, SD 1.11) ($p < 0.05$). The INR values by POC-T method were significantly correlated to the laboratory method ($r = 0.875$, $p<0.01$). The INR values measured by POC-T exhibited positive bias as the INR values increased, particularly when INR readings were higher than 4.0.

Conclusion: Our findings suggested that POC device is a reliable tool for INR monitoring when the INR value is below 4.0. As the INR values generated by the POC-T device exhibited bias at higher INR values, a repeat test using laboratory method must be considered when the INR is 4.0 or higher.

Keyword: warfarin, INR, POC-T

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Corresponding author: Nurul Najmi Binti Muhammad
Department of Pharmacy, Hospital Sultanah Nur Zahirah, Jalan Sultan Mahmud, 20400 Kuala Terengganu, Terengganu
Email: nurulnjm@gmail.com

Introduction

Warfarin is one of the oral anticoagulation drugs most commonly prescribed for atrial fibrillation, heart valve replacement or venous thromboembolism (1). Meticulous monitoring of patients receiving warfarin therapy is important due to the drug's narrow therapeutic range, which is typically measured by the International Normalised Ratio (INR). Sub therapeutic anticoagulation can increase the risk of clot formation, thus increasing the chance of stroke or venous thromboembolism, while supra therapeutic anticoagulation increases the risk of bleeding.

The standard method for INR monitoring is laboratory testing of blood obtained by venipuncture. The blood samples are collected into citrate tubes, centrifuged and plasma is loaded on to coagulation analyser. The time taken from the time patient walks in to the laboratory to reporting is approximately 40 – 60 minutes. Alternatively, there is an easier method to monitor INR value which is using the point-of-care (POC) device. POC testing (POC-T) for INR involves putting a sample of whole blood, usually capillary blood from a finger

prick, onto a test strip. The INR result will be produced within two minutes and this is much faster as compared to the laboratory-based method. The immediate results obtained using POC-T will allow rapid adjustment of warfarin dose as compared with more complex laboratory-based method (2-4). This will increase patient convenience, improve the clinical outcomes, reducing patients' waiting time in clinic and reduce health care resources use. However, there have been several documented limitations regarding the accuracy and precision of POC devices. Previous studies (5,6) found that INR measurements generated by POC device exhibit positive bias when compared with the laboratory-based method as INR values increased. Having a predetermined INR cut-off value for mandatory venipuncture and laboratory-based method in INR determination may potentially decrease the frequency of avoidable thromboembolic events and improve patient safety.

In Sultanah Nur Zahirah Hospital (HSNZ), Kuala Terengganu, patients that receive warfarin therapy will be referred to the INR clinic for their follow up visits. The INR clinic is currently managed by a pharmacist, which is also called as a Medication Therapy Adherence Clinic (MTAC), and supervised by the Medical Officer of Medical Department HSNZ. During the clinic visits, the pharmacist manages the appointments, interviews and counsels the patient, performs finger prick tests to measure patient's INR on a POC device, adjusts warfarin dose based on the INR values, refers patients to doctors if indicated, and completes all appropriate documentations.

There are two types of INR testing used in HSNZ which are clinic-based POC testing and laboratory-based testing. In the clinic-based testing, finger prick will be done by the clinic pharmacist to obtain a drop of blood to be put onto the POC device (Coaguchek XS Pro ®, Roche Diagnostics, Indianapolis, Indiana) and the INR result will be obtained within 2 minutes. The INR result will be recorded in the patient's Electronic Medical Record (EMR) in Hospital Information System and Patient's Attendance Book (*Buku Kehadiran Pesakit*). In the laboratory-based testing, venous blood sample will be taken by venipuncture and sent to the laboratory to be analysed using the STAGO STA Compact ® (Diagnostica STAGO Inc, Parsippany, New Jersey). INR result with laboratory method will be obtained within an hour and reported in the patient's EMR. As a routine procedure of INR clinic, POC and laboratory INR will be done for an average of five patients on the same day of every month to monitor the performance of the POC device. As part of the INR clinic's procedure, any patient whose POC-measured INR exceeded 4.0 will have a venipuncture sample sent to the laboratory to double confirm the INR value. In this case, INR measured by laboratory method will be used to guide warfarin dose adjustment.

The data from our routine monitoring of the POC device in the INR clinic from September 2016 to December 2016 highlighted that out of 127 patients whose POC-measured INR were higher than 4.0, the confirmatory INR results using the laboratory method showed that 31.5% of the patients have the INR value within therapeutic range. Because of that, the patient safety might be compromised since clinicians might reduce the warfarin dose if the confirmatory test with laboratory method was not done leading to increased risk of thromboembolic events. Thus, this study aimed to compare the INR results obtained by the POC-T with laboratory based method and to determine the cut-off point for INR values generated by the POC-T device that should mandate confirmatory testing with the laboratory method.

Methods

Study Design and Population

This cross-sectional study was conducted at HSNZ, Kuala Terengganu. Data of patients were reviewed retrospectively. This study included patients who attended the INR clinic of HSNZ between 1 June 2016 and 30 May 2017. The inclusion criteria were patients aged at least 18 years old, who had their INR values tested by both the POC-T method and laboratory-based method on the day which the routine procedure was conducted every month to monitor the POC device. The exclusion criteria were pregnancy and POC INR result higher than 8.0 at the time of assessment since the POC device cannot measure INR more than 8.0.

The POC device used in the INR clinic of HSNZ was Coaguchek XS Pro ® (Roche Diagnostics, Indianapolis, Indiana) while the standard laboratory analyser in the HSNZ laboratory was STAGO STA Compact ® (Diagnostica STAGO Inc, Parsippany, New Jersey).

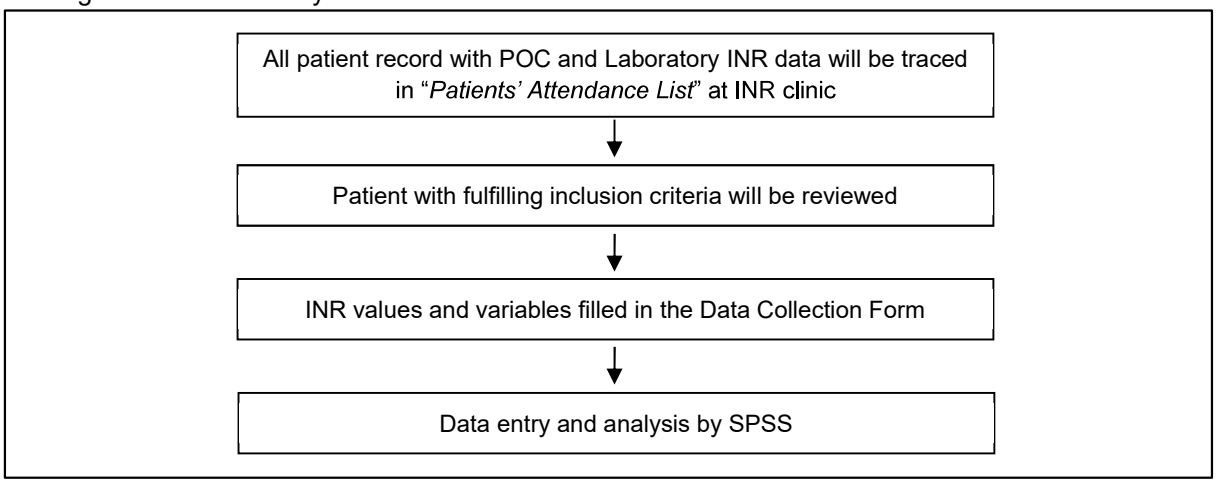
Data Collection and Analysis

Data collection was carried out over 2 months from 15 July 2017 to 15 September 2017. The "*Patients' Attendance List*" maintained at the INR clinic was checked to identify all patients with both POC and laboratory INR data between 1 June 2016 and 30 May 2017. Patients fulfilling the study criteria were included as the subjects for this study.

A specified data collection form was used for data collection. The required information were collected from the patients' EMR in the HIS system. The variables collected for this study were age, gender, race, indication of Warfarin, INR target range and both POC and Laboratory INR values. The INR values that were obtained using the POC device in the INR clinics were collected from the clinic's "*Patients' Attendance List*" while the INR value obtained using the laboratory-based method were traced electronically from the patients' EMR in the HIS system.

The INR results were compared using Pearson correlation and Bland-Altman plot. Data was analysed using SPSS v.20 with $p<0.05$ was considered statistically significant. The flow of the study was summarised in Figure 1.

Figure 1: Flow of study



Results

The data of 118 subjects were collected and 236 or 118 pairs of INR readings were analysed. The mean age of the included patients was 60.7 years old (standard deviation (SD) 14.8). The demographics of the populations evaluated were listed in Table 1. The mean INR values of the POC-T method and laboratory method were listed in Table 2. There was a statistically significant difference between the INR values obtained by the POC-T (3.87, standard deviation (SD) 1.71) and laboratory-based method (2.88, SD 1.11) ($p < 0.05$).

Figure 2 showed the correlation between INR values obtained with POC-T and laboratory method. The INR values of the POC-T were significantly correlated with the laboratory INR values ($r = 0.875$, $p < 0.01$). Even though good correlation was obtained, the use of the correlation coefficient may be misleading in comparing the agreement between the two methods of INR analysis. Therefore, the Bland-Altman plot was used to compare the INR results obtained by these two methods.

The Bland-Altman plot showed that POC-T tended to overestimate the INR compared to the laboratory-based method and the degree of overestimation increased as the INR value increased. The two methods had better agreement (less scattered) when the INR values were less than 3.0. The plots were more scattered and there were more outliers, which meant that the two measurements were less comparable, when the INR values were higher than 4.0. The mean differences calculated showed agreement with the rough variations formula given by the POC device provider (7) (Table 3).

Table 1: Patient demography (N=118)

Parameter	Frequency
Age, years, mean (SD)	60.7 (14.8)
Gender, n (%)	
Female	64 (54.2)
Male	54 (45.8)
Race, n (%)	
Malay	112 (94.9)
Chinese	6 (5.1)
INR Target, n (%)	
2.0 – 3.0	100 (84.7)
2.5 – 3.5	17 (14.4)
3.0 – 4.0	1 (0.8)
Indication, n (%)	
Atrial fibrillation	83 (70.3)
Heart valve replacement	17 (14.4)
Deep vein thrombosis	7 (5.9)
Pulmonary embolism	2 (1.7)
Left ventricular clot	5 (4.2)
Antiphospholipid syndrome	3 (2.5)
Occlusion of Fontan	1 (0.8)

Abbreviation: INR – International Normalised Ratio; SD – standard deviation

Table 2: INR values by POC-T and laboratory method

Parameter	POC-T	Laboratory	p value
INR, mean (SD)	3.87 (1.71)	2.88 (1.11)	$p < 0.05$ [b]
Difference, mean (SD) [a]	0.98 (0.91)		

[a] t-test, [b] statistically significant

Abbreviation: INR – International Normalised Ratio; POC-T – point-of-care testing

Figure 2: Pearson correlation between INR values obtained with POC-T and laboratory-based method

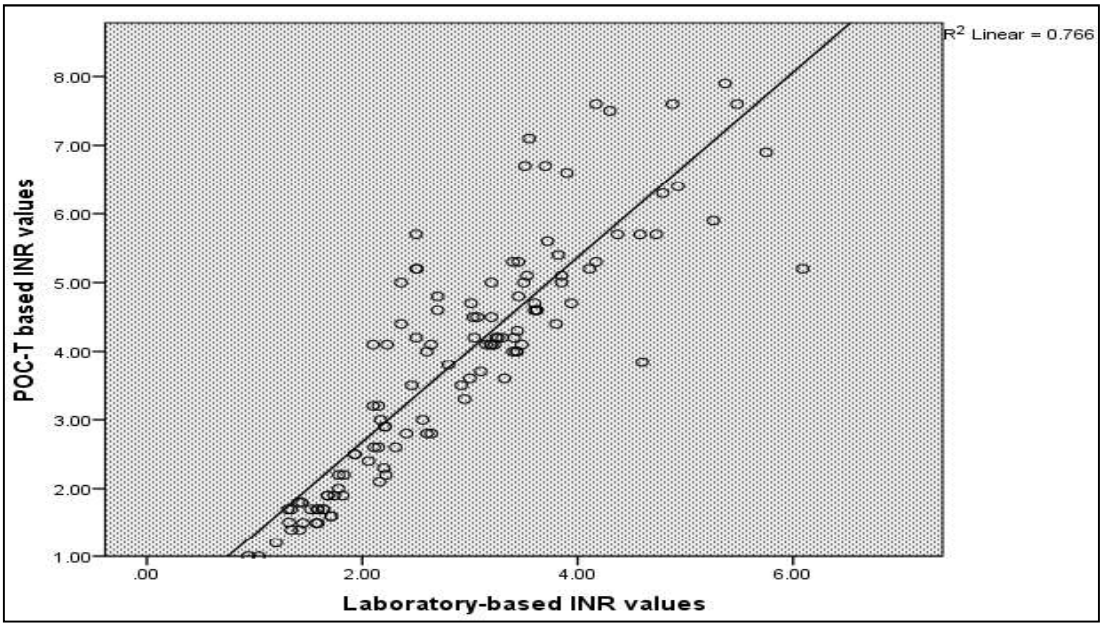


Figure 3: The Bland-Altman plot comparing the INR values measured by POC-T and laboratory-based method

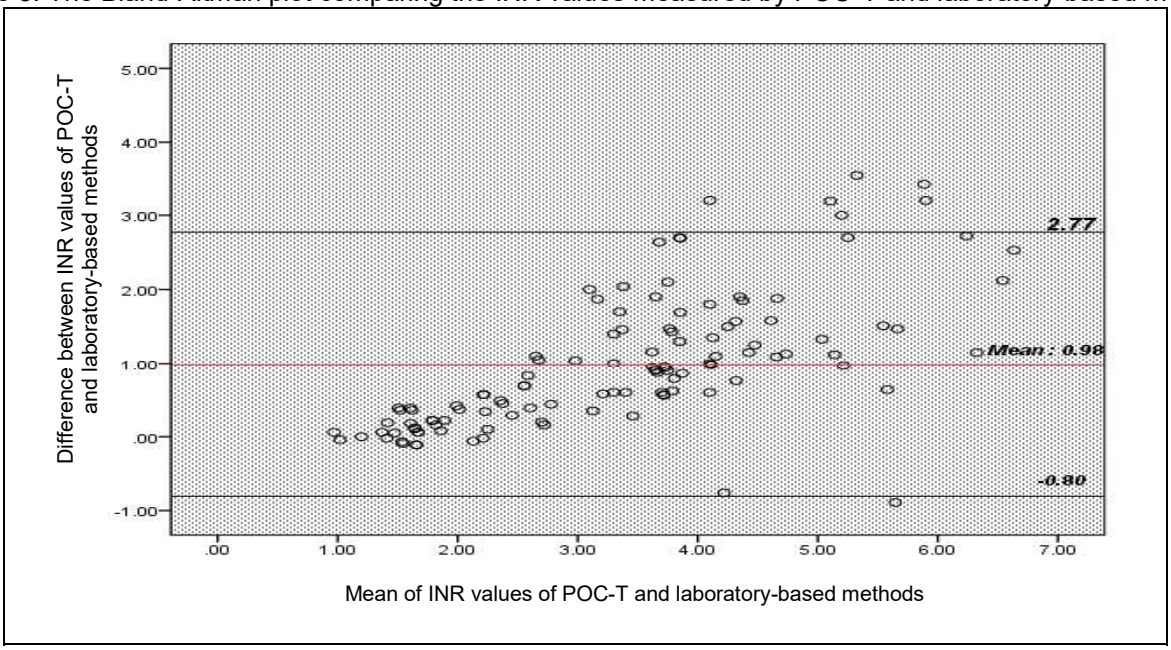


Table 3: Mean differences calculated in INR ranges compared with the rough variation formula

INR	Mean INR		INR Difference	Rough variation [a]
< 2.5	POC LAB	1.71 1.58	0.13	0.1-0.3
2.5 – 4.5	POC LAB	3.67 2.89	0.78	0.5-1.0
> 4.5	POC LAB	5.59 3.77	1.82	1.0-2.0

[a] provided by the POC device provider (7)

Discussion

Donaldson *et al*. reported that the INR values measured by POC-T device correlated well with the laboratory testing, with the correlation coefficient (r) of 0.949 (6). In comparison, we calculated a lower correlation coefficient of 0.845. Our analysis of 118 paired of INR samples included 29 pairs that differed by more than 1.0 unit, thus skewed the overall correlation analysis. Nevertheless, the correlation coefficient of 0.875 has shown that the INR values obtained using POC device and laboratory-based method had strong positive correlation. Even though POC-T and laboratory method has a strong correlation, there was a disagreement between the two methods as shown by the t-test, and the Bland-Altman plot was used to show where the disagreement occurred.

In this study, we found that the INR values measured by POC device exhibited positive bias as the INR values increased, especially when INR values were higher than 4.0. Out of the 65 POC-T measured INR readings that were 4.0 or higher, 41.5% of the repeated assessment with laboratory method had shown that the INR values were actually within the therapeutic range. This observation may have potentially profound clinical implications. Without the awareness of positive bias, clinicians might reduce the dose of warfarin based on POC-T measurement and this could lead to the increased risk of thromboembolic events.

The Bland-Altman plot showed that the POC-T tended to overestimate the INR compared to the laboratory measurement and the degree of overestimation increased as the INR values increased. Our results were consistent with other previous studies which also observed positive bias of INR measurements when comparing the POC-T and laboratory-based method (5-6,8). However, we found more outliers with more scattered Bland-Altman plot when the INR values were greater than 4.0, as compared to other studies. The

factors that influence the INR values includes genetic, diet, concomitant disease and other concurrent medications (9,10).

Despite the positive bias that may happen when the INR is above 4.0, the POC-T is a suitable alternative to the laboratory assessment of INR as they have comparable accuracy and the measured INR values were found to be in agreement with the laboratory-measured INR values when the INRs were below 4.0 (8). POC devices will increase patient convenience and can help to reduce healthcare resources. Based on our study finding that was consistent with the previous study (5), an INR of 4.0 should be recommended as the cut-off point that mandates a repeated INR test using the laboratory method.

Conclusion

The findings of this study suggested that the POC device is a reliable tool for INR measurement when the INR is lower than 4.0. As the INR values generated by POC-T device may exhibit bias at INR more than 4.0, a repeated test using the laboratory method should be made mandatory when INR is above this value.

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