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Point-of-Care versus Standard Laboratory Method for International Normalized Ratio Testing in a Pharmacy-managed Anticoagulation Clinic

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***Abstract*— Introduction:** *Point-of-care (POC) testing devices are increasingly being used in the clinical setting. They are convenient as the tests can be performed in a pharmacy-managed anticoagulation clinic to provide rapid results compared to the standard laboratory method. Therefore, we aimed to determine the agreement between international normalized ratio (INR) levels obtained from a POC device and laboratory instrument.* **Methods:** *In a pharmacist-managed anticoagulation clinic, 20 patients receiving oral warfarin therapy had their INR levels measured using a POC device, CoaguChek® XS. During the same visit, another blood sample was collected from each patient for INR measurement and sent to the laboratory in Hospital Raja Perempuan Zainab II, Kelantan. The linear relationship and agreement between INR levels obtained from both methods were analysed using Pearson's correlation and Bland-Altman plot in Statistical Package for Social Sciences (SPSS) version 22.0.* **Results:** *The mean (SD) INR levels obtained from POC device and standard laboratory were 2.54 (1.30) and 2.27 (1.01), respectively. There was a significant strong positive correlation between the INR levels obtained from the two methods ($r= 0.983$, $p<0.001$). Also, a good agreement was observed between POC device and standard laboratory when INR levels were less than 3.0. Only 1 value at 6.94 fell out of 95% CI.* **Conclusion:** *The INR levels obtained from the POC device were comparable to the standard laboratory especially in an outpatient setting. However, in cases whereby the INR levels are in the supratherapeutic range, it is recommended to carry out a laboratory test for result confirmation before any clinical interventions are done.*

Keywords*—International normalized ratio, pharmacy-managed anticoagulation clinic, warfarin, point-of-care, laboratory*

I. INTRODUCTION

Oral anticoagulation therapy has been a treatment for both prophylactic and therapeutic use in patients at risk of developing thromboembolism [1]. Warfarin is the most commonly used medication to treat and prevent blood clots by supressing the production of vitamin K clotting protein. The dose-response of warfarin among patients is highly variable and depends on interpatient differences. Patient-specific factors such as drug metabolism, the presence of a vitamin K enriched diet, genetics, quantity of vitamin K-dependent clotting factors, concurrent disease states, binding proteins, concomitant drug interactions, laboratory testing, and medication adherence requires assessment when starting warfarin [1]–[3].

Because of the variations in doses needed for each patient, warfarin requires frequent laboratory monitoring and dose adjustment to maintain blood levels within the target range called the international normalized ratio (INR) [1]–[3]. INR of 2.0 to 3.0 is compulsory to make sure patient are in a narrow therapeutic index to prevent clot formation that would lead to blockage in veins inside the body. Patients taking oral anticoagulants are required to monitor INR to adjust the warfarin doses because these vary between patients [1]–[4].

The usual method for monitoring drug therapy is laboratory testing of blood obtained by venepuncture to measure the INR [5]. Another way of INR monitoring is by point-of-care (POC) testing; a test which is performed at or near where a patient is located [5] such as a pharmacy-managed anticoagulation clinic [6]–[8]. It requires only a small sample of blood which is obtained by pricking the fingertip. The blood is placed on a test strip and inserted into a device called a coagulometer, which analyses the blood and displays the INR result [5].

Nowadays, POC testing is widely used due to its reliable and rapid results. Evidences have shown that POC testing is a convenient alternative for INR monitoring as it contributes to patient satisfaction with shorter waiting time. A potentially more timely clinical decision-making can improve the clinical outcomes and reduce health care resource use [9]–[12].

However, there were some biases and disagreements reported when both methods were compared [11]. Curtis et al. (2012) emphasized the need for frequent and continuous evaluation of the INR results obtained from POC device especially during the change of equipment [9]. As for Sephel and Laposata (2013), they observed that even after a long period of correlation, transiently increased variation could be seen between both methods [13]. Hence, to ensure proper anticoagulation management, we aim to determine the agreement between INR levels obtained from a POC device and laboratory instrument in a pharmacy-managed anticoagulation clinic at a tertiary care hospital in Kelantan, Malaysia.

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II. METHODS

A. Design and Study Population

A cross-sectional study was carried out from November 2019 to November 2020. The inclusion criteria were adult patients attending the pharmacy-managed anticoagulation clinic, Hospital Raja Perempuan Zainab II with routine INR monitoring appointments. Those with INR levels of more than 8.0, pregnant or admitted into the wards were excluded.

B. Data Collection

Eligible subjects were approached at the clinic and were invited to join the study. They were explained regarding the research procedure and were given ample time to read through the information sheet. Those who consented were recruited into the study using convenience sampling.

The methods used were CoaguChek® XS as the POC device and standard laboratory. Two drops of capillary whole blood and three ml of venous blood were collected from each subject. The capillary blood testing was taken by finger prick method by the pharmacist-in-charge of the clinic and tested using the POC device. For the venous sampling, it was performed by a trained phlebotomist and samples were sent to the laboratory where INR testing was performed within two hours of sample collection. Both capillary blood testing using the POC device and standard laboratory method were determined in duplicate. The results were then collected and compiled in a data collection form along with demographic and clinical characteristics of the subjects.

C. Statistical Analysis

The data analysis was performed using Statistical Package for Social Sciences (SPSS) version 22.0. The demographic and clinical characteristics of the subjects were expressed in frequencies and percentages. Paired t-test was used to compare mean (SD) INR levels from both methods while Pearson's correlation was used to measure their linear relationship. Finally, Bland-Altman plot was utilized to determine the agreement between INR levels obtained from a POC device and laboratory instrument. Statistical significance was set as p-value of less than 0.05.

D. Ethical Approval

The study was registered with National Medical Research Register (NMRR), Ministry of Health Malaysia (NMRR-20-1724-54465). The ethical approval was gained from Medical Research and Ethics Committee (MREC), Ministry of Health Malaysia while the permission to conduct it was obtained from the hospital director. All subjects were remained anonymous to ensure their confidentiality.

III. RESULTS

A. Demographic and Clinical Characteristics

A total of 20 patients were recruited within the data collection period. They were mostly of the age less than 65 years old (70.0%, n=14), female (55.0%, n=11) and Malay ethnicity (95.0%, n=19) (Table 1).

TABLE 1. Demographic characteristics of study population.

Characteristics	n	%
Age (years old)		
<65	14	70.0
≥65	6	30.0
Gender		
Male	9	45.0
Female	11	55.0
Ethnicity		
Malay	19	95.0
Non-Malay	1	5.0

As for the clinical characteristics, most of the patients were prescribed with lifelong warfarin for atrial fibrillation (90.0%, n=18) and had INR target of 2.0 to 3.0 (55.0%, n=11) (Table 2).

TABLE 2. Clinical characteristics of study population.

Characteristics	n	%
Indications		
Atrial fibrillation	18	90.0
Others	2	10.0
INR target		
2.0 to 3.0	11	55.0
2.5 to 3.5	7	35.0
Others	2	10.0
Duration of therapy		
3 months	1	5.0
6 months	1	5.0
Lifelong	18	90.0

B. INR Levels

Comparison of Mean (SD) INR Levels

The mean (SD) INR levels measured by POC device was 2.54 (1.30) and 2.27 (1.01) using the standard laboratory instrument. There was a statistically significant difference between both mean (SD) INR levels (p=0.004) (Table 3).

TABLE 3. Comparison of INR levels obtained from POC device and standard laboratory

Methods	Mean (SD)	Mean difference (95% CI)	p-value
POC device	2.54 (1.30)	0.27 (0.10, 0.43)	0.004
Laboratory	2.27 (1.01)		

Paired t-test

Correlation of INR Levels

Further analysis also showed that there was a statistically significant strong positive correlation between INR levels obtained by both methods (r= 0.983, p<0.001) (Table 4 and Figure 1).

TABLE 4. Correlation between INR levels obtained from POC device and standard laboratory.

Methods	Laboratory	p-value
POC device	0.983	<0.001

Pearson's correlation

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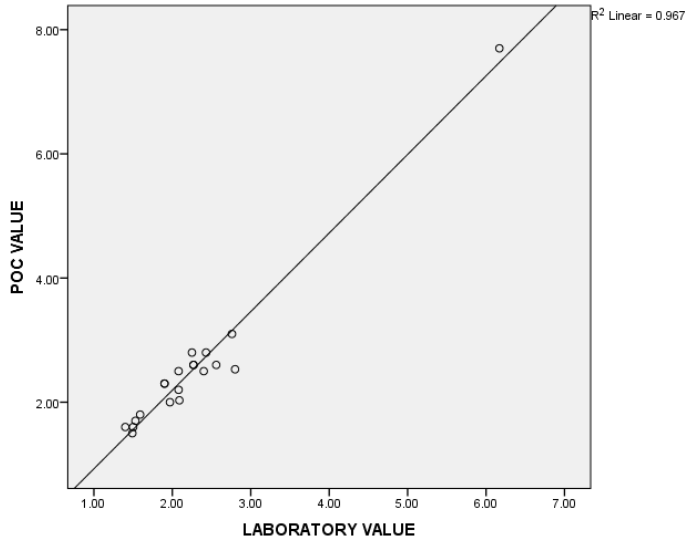

Figure 1. Scatter plot for INR levels obtained from POC device and standard laboratory

Agreement between INR Levels

There was a good agreement between INR levels obtained from POC device and standard laboratory. All INR levels which were less than 3.0 were within 95% CI. Only 1 value at 6.94 fell out of the range (Figure 2).

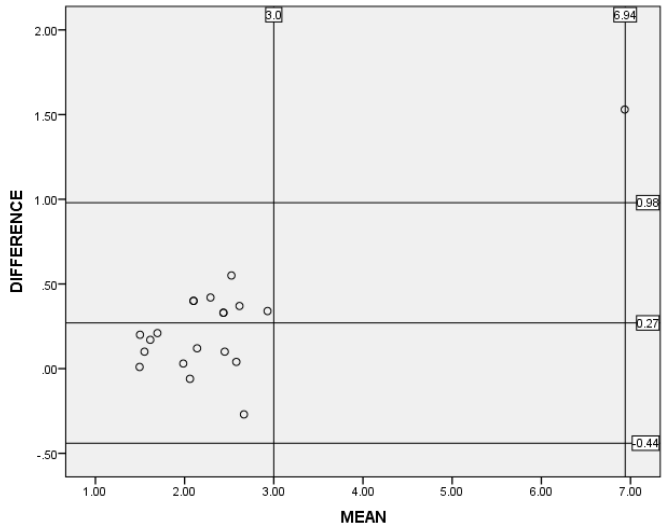

Figure 2. Bland-Altman plot for INR levels obtained from POC device and standard laboratory POC.

IV. DISCUSSION

Frequent blood monitoring of INR can be traumatic especially for patient who are in long term or lifelong warfarin therapy. The emergence of the advance technology such as POC have offers significant advantages for patient in terms of waiting time and its less invasive procedure for blood taking which would greatly influence the patient's compliance to INR monitoring [8], [11], [14].

The present study showed statistically significant difference between mean (SD) INR levels between POC and standard laboratory method. This finding the same as Donaldson et al. (2010) which reported the mean (SD) difference between INR levels between CoaguChek® XS Plus (POC device) and STAGO (laboratory instrument) was 0.27 [6]. Other consistent study was Moiz et al. (2018) who noted that the mean (SD) difference between INR levels generated with CoaguChek XS Pro (POC device) and Sysmex CS 2000i (laboratory instrument) was 0.21 [15]. A more recent local study by Ab Aziz and Awang (2019) also observed a significant mean difference of 0.32 between INR obtained from the two methods. However, it is important to take into account that a statistically significant difference does not necessary mean clinically significant [16]. The clinician must consider the INR target for each patient as the dosing decision based on POC device may be different from that of laboratory instrument [15].

Most previous literature described congruous correlation pattern between INR levels obtained by both methods. Our finding was in line with these results whereby they observed a significant strong relationship with Pearson's correlation coefficient of more than 0.9. Such examples recorded were r=0.973 (p<0.001) by Moiz et al. (2018) in 200 measurements [15], r= 0.941 (p<0.001) by Ab. Aziz and Awang (2019) in 52 patients [16], r=0.919 (p<0.001) by Palaparti et al. (2020) [17] in 205 samples. This showed that the overall relationship of the INR measurements between both methods was excellent and without significant deviation from linearity.

Overall, the present study found that there was a good agreement between INR levels obtained from POC device and standard laboratory. Only 1 INR level measured at 6.94 fell out of 95% CI. Similar observations were made by a number of studies that showed an increased INR difference at higher INR values. Baker et al. (2017) conclude that the agreement was significantly less at high INR levels or supratherapeutic range [18]. Ab Aziz and Awang (2019) reported there was a good agreement and consistency between both methods when INR levels were less than 3.5. As the INR levels went up, the discrepancies between the measurements became bigger and most values fell out of 95% CI [16]. In another investigation, Bhat et al., (2020) noted a drift in POC testing when INR values were greater than or equal to 4.7 [12]. Biedermann et al. (2015) observed at INR levels of more than 4.0, the difference between the paired measurements was the highest (47.8%) [19]. This indicated that INR levels obtained from POC device are usually comparable to that of conventional laboratory testing except when in supratherapeutic INR range.

Even though the accuracy of POC device might be biased in high INR as the previous studies demonstrated, Lawrie et al. (2012) found that POC device was accurate even in high INR results. They suggested that it was probably unnecessary to perform laboratory INR for clinical decisions in patients with INR range of 4.5 to 8.0 [20]. Having said that, in view of the discrepancies reported in previous study, in clinical practice it is perhaps safer to complete a laboratory test in high INR values for result confirmation.

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A limitation of this study was the small sample size achieved in a single center setting. Only one INR value was above 3.0. Therefore, the findings should be interpreted cautiously as it did not represent the whole study population. Future investigation with equal randomization in different INR ranges is warranted to portray the actual performance of POC device.

V. Conclusion

With the strong, positive correlation and good agreement, it can be concluded that the INR levels obtained from the POC device were comparable to the standard laboratory especially in an outpatient setting. However, in cases whereby the INR levels are in the supratherapeutic range, it is recommended to carry out a laboratory test for result confirmation before any clinical interventions are done.

Conflict of Interest

The authors declare that they do not have any personal or financial conflict of interest that may arise from the research publication.

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