COMPARISON OF INTERNATIONAL NORMALIZED RATIO (INR) BETWEEN POINT OF CARE DEVICE COAGUCHEK® XS VERSUS STANDARD LABORATORY INSTRUMENT AMONG PATIENTS RECEIVING WARFARIN THERAPY IN A NORTHEAST STATE OF PENINSULAR MALAYSIA.

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ABSTRACT

Background: Warfarin is widely used and cost-effective for various indications. However, the narrow therapeutic index of warfarin requires frequent International Normalized Ratio (INR) monitoring. The purpose of this study was to compare the mean differences, to examine the correlation and agreement between the two methods of venipuncture using laboratory assay and by finger prick using Point of Care (POC) device (CoaguChek® XS).

Materials and Methods: A cross sectional study was done in warfarin Medication Therapeutic Adherence Clinic (MTAC), Kuala Krai Hospital. Convenient sampling was used to recruit patients from August until December 2016. The INR results from CoaguChek® XS were compared with the results from standard laboratory assay. Descriptive statistics, paired t-test, Pearson's correlation and Bland-Altman plot were used for data analysis.

Result: A total of 52 patients with 84 paired samples were collected in this study. The mean INR values obtained from CoaguChek® XS was significantly different from standard laboratory method (p<0.001). However, there was a strong positive correlation between these two methods (r=0.941, p<0.001). Besides, Bland-Altman plot demonstrated a good agreement between both methods especially when INR values less than 3.5.

Conclusion: Despite the mean differences of INR values between these two methods was statistically significant, but it was clinically not significant (mean difference = 0.32). There was a strong correlation and good agreement between INR values obtained from these two methods. These findings may help clinicians in improving the quality of INR monitoring for patients on warfarin therapy.

Keywords: Point of Care device, standard laboratory method, INR, warfarin.
1.0 Introduction

Warfarin has been widely used as oral anticoagulant which works by inhibiting the synthesis of vitamin K-dependent clotting factors (Ansell et al., 2008). It is prescribed for both prophylactic and therapeutic use in patients at risk of thromboembolism. The common indications for warfarinisation to prevent thromboembolism are atrial fibrillation, venous thromboembolism and prosthetic heart valves (Tadros & Shakib, 2010).

Nevertheless, warfarin therapy requires frequent monitoring due to narrow therapeutic range, variability in dose response among patient and the risk of over- and under-dosing of anticoagulation which can be life threatening (Curtis et al., 2012). Inadequate anticoagulation lead to thromboembolic events, while patient that receive excessive anticoagulation are at risk of bleeding (Fihn et al., 1993). Monitoring is based on the International Normalized Ratio (INR), a calculation based on results of a prothrombin time (PT) that checks how long it takes for blood to clot (Lakshmy & Kumar, 2010). The higher the INR, the longer it will take blood to clot and the lower the INR, the more likely to develop a blood clot (Dorfman et al., 2005).

Conventionally, INR is determined on citrated plasma obtained by venipuncture using laboratory method. Laboratory PT/INR testing in plasma is the method of choice for monitoring anticoagulant therapy. For laboratory testing of INR, blood samples are collected by venipuncture and sent to laboratory for centrifugation and the citrated plasma used for standard laboratory prothrombin time (Hentrich et al., 2007) The time taken from the time patient walks in to the laboratory until to get the result is approximately 25 to 30 minutes which is quite lengthy (Ferring et al., 2001; Iijima et al., 2014) Moreover, patients on warfarin therapy require serial INR measurements to monitor for the warfarin effectiveness. Over the time, an approach to improve the monitoring of anticoagulant therapy was recently available with the use of point of care devices. Convenience of INR measurement can be increased if testing could be performed with less frequent visit to the laboratory and with a relatively easier method which is Point of Care (POC) testing (Lakshmy & Kumar, 2010).

INR monitoring by Point of Care (POC) device is relatively less invasive which only require finger prick and is fast in producing results (less than 2 minutes) as compared to standard laboratory measurement. CoaguChek® XS is one of the POC testing devices and it is a small, battery-powered, handheld meter that is portable and efficient. It measures the INR using whole blood obtained by capillary puncture (Lakshmy & Kumar, 2010).

The procedure involves insertion of a test strip into the monitor and application of a drop of blood (minimum of 8μL) onto the test strip. The monitor uses an electrochemical method to determine the prothrombin time (PT) after activation of coagulation with a recombinant human thromboplastin within the test strip. The mean international sensitivity index (ISI) for the CoaguChek® XS prothrombin time test is 1 (Roche Diagnostics, 2016). The PT is then converted to an INR using the ISI that was previously determined and encoded on the chip for each lot of test strips. The INR result is usually provided in less than 2 minutes, approximately 10 seconds after application of blood to the test strip (Iijima et al., 2014).

However, accuracy and reliability of the point of care results is critical. Disagreement between Point of Care (POC) and standard laboratory testing could impose confusion in warfarin dosage decision making and anxiety for both patients and healthcare providers.
(Sunderji et al., 2005). Inadequate doses lead to thromboembolic events and patients that receive excessive anticoagulation are at risk of bleeding (Dorfman et al., 2005). Therefore, this study was aimed to investigate differences in INR values obtained by POC and laboratory method, to determine correlation and evaluate the agreement between the INR values obtained by POC and laboratory method in order to help clinicians in improving the quality of INR monitoring among patients on warfarin therapy.

2.0 Materials and Methods

This study applied a cross-sectional study design and was conducted within five months period starting from August 2016 to December 2016 in Kuala Krai Hospital, Kelantan state. Kuala Krai Hospital is one of the biggest and sophisticated hospitals in northeast region of Peninsular Malaysia and its pharmacy department has an “INR clinic” to provide comprehensive INR monitoring services for patients on warfarin therapy.

The reference populations were all patients under warfarin therapy in Kelantan and the study samples were patient receiving warfarin therapy who were under medication therapy adherence clinic (MTAC) follow-up by pharmacists at Kuala Krai Hospital which fulfilled study inclusion and exclusion criteria. In this study, the inclusion criteria were adult patients aged 18 years old and above and patient under Warfarin MTAC follow-up. Pregnant patient, warded patient and patient with INR reading more than 8.0 were excluded from this study.

Convenient sampling was the sampling method of choice. A total of 58 patients attending Warfarin MTAC follow-up at Kuala Krai Hospital were traced through records of patients. After considering the inclusion and exclusion criteria, only 52 patients were eligible to participate in the study. All patients who agreed to undergo both venous and finger prick samplings were invited and counselled about the study to obtain consent. In each patient’s visit, the clinic used two methods routinely to obtain INR results which are POC and standard laboratory. In this study, researcher collected INR results from these two methods for further analysis.

Information collected from patients were socio-demographic characteristics (age, gender, and race), clinical characteristics (indication of warfarin, duration of treatment and target range for INR) and INR reading from both methods which are point of care device, CoaguChek® XS and standard laboratory. During each visit, consented patients need to undergo venipuncture after register the attendance at the clinic. It was done by a trained staff nurse to collect the blood and then the blood was sent to laboratory. After that, capillary blood was taken by finger prick method by a pharmacist-in-charge to generate INR values using the point of care device (CoaguChek® XS). The flowchart for this study is shown in Figure 1.

Data were analyzed by using SPSS software version 20. The categorical data were represented in frequency and percentage. The differences between INR values generated by POC device (CoaguChek® XS) and standard laboratory methods were measured by using paired t-test. A p-value of less than 0.05 was considered significant. Apart from that, Pearson’s correlation was conducted to identify the correlation between these two methods.
The agreement of INR values between point of care device and standard laboratory measurement was assessed by using Bland-Altman plot.

![Flowchart of study](image_url)

**Figure 1:** Flowchart of study
3.0 Result

A total of 52 patients were selected in this study. The female patients were found to be in greater proportion compared to male patients which is 63.5% and 36.5% respectively. The mean age of patients were 56.67 year and majority of them were of adult group with 65.4%. Out of 52 patients, Malay was the predominant ethnic group in this study which was 47 patients (90.4%). Details regarding socio-demographic characteristics of patients were shown in Table 1.

Table 1: Socio-demographic characteristics of patients under Warfarin MTAC follow-up at Kuala Krai Hospital (n=52)

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Frequency (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>19 (36.5)</td>
</tr>
<tr>
<td>Female</td>
<td>33 (63.5)</td>
</tr>
<tr>
<td>Age (years)</td>
<td>56.67 (13.79)*</td>
</tr>
<tr>
<td>Adult (18-64)</td>
<td>34 (65.4)</td>
</tr>
<tr>
<td>Elderly (65 and above)</td>
<td>18 (34.6)</td>
</tr>
<tr>
<td>Race</td>
<td></td>
</tr>
<tr>
<td>Malay</td>
<td>47 (90.4)</td>
</tr>
<tr>
<td>Others</td>
<td>5 (9.6)</td>
</tr>
</tbody>
</table>

*Mean(SD)

As for clinical characteristics, out of 52 patients, 63.5% used warfarin for atrial fibrillation, 9.6% for venous thromboembolism, 17.3% for mechanical valve replacement, and 9.6% were using warfarin for other indications. Most patients had the INR target of 2.0 to 3.0 (73.1%) followed by others target which is 15.4% and lastly INR target of 2.5 to 3.5 which is 11.5%. The mean weekly dose of warfarin per patient was 23.18 mg. As for INR reading, the mean INR value by POC reading was 2.41 and by laboratory reading was 2.09. Details regarding clinical characteristics of patients were shown in Table 2.
Table 2: Clinical characteristics of patients under Warfarin MTAC follow-up at Kuala Krai Hospital (n=52)

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Frequency (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Indications</strong></td>
<td></td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>33 (63.5)</td>
</tr>
<tr>
<td>Deep vein thrombosis</td>
<td>5 (9.6)</td>
</tr>
<tr>
<td>Valve replacement</td>
<td>9 (17.3)</td>
</tr>
<tr>
<td>Others</td>
<td>5 (9.6)</td>
</tr>
<tr>
<td><strong>INR target</strong></td>
<td></td>
</tr>
<tr>
<td>2.0 – 3.0</td>
<td>38 (73.1)</td>
</tr>
<tr>
<td>2.5 – 3.5</td>
<td>6 (11.5)</td>
</tr>
<tr>
<td>Others</td>
<td>8 (15.4)</td>
</tr>
<tr>
<td><strong>Total weekly dose (mg)</strong></td>
<td>23.18 (8.90)</td>
</tr>
<tr>
<td><strong>INR reading by CoaguChek® XS</strong></td>
<td>2.41 (1.29)</td>
</tr>
<tr>
<td><strong>INR reading by laboratory</strong></td>
<td>2.09 (0.86)</td>
</tr>
</tbody>
</table>

*Mean (SD)

The differences in INR values obtained by POC and standard laboratory method were calculated using paired t-test. The result showed a statistically significant difference of mean INR between point of care device, CoaguChek® XS and standard laboratory (p-value <0.001) as shown in Table 3.
Table 3: Differences of the mean INR between point of care device, CoaguChek® XS and standard laboratory among patients under Warfarin MTAC follow-up at Kuala Krai Hospital (n=52)

<table>
<thead>
<tr>
<th>Methods</th>
<th>Mean INR (SD)</th>
<th>Mean Difference (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CoaguChek® XS</td>
<td>2.41 (1.29)</td>
<td>0.32 (0.20, 0.44)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Standard laboratory</td>
<td>2.09 (0.86)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Paired t-test

The strength of the relationship between two methods was assessed using Pearson correlation coefficient. There was strong positive correlation between INR value obtained by CoaguChek® XS and standard laboratory which was statistically significant (r= 0.941, p<0.001) as shown in Table 4 and Figure 2.

Table 4. Correlation between point of care device, CoaguChek® XS INR reading and standard laboratory INR reading among patients under Warfarin MTAC follow-up at Kuala Krai Hospital (n=52)

<table>
<thead>
<tr>
<th>Methods</th>
<th>CoaguChek® XS INR reading</th>
<th>Pearson’s correlation</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Standard laboratory INR reading</td>
<td>0.941</td>
<td></td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

*Pearson’s correlation
Figure 2: Correlation of INR reading between point of care device, CoaguChek® XS and standard laboratory measurement
The agreement between two methods was assessed using Bland-Altman plot. There was a good agreement between both methods when INR value less than 3.5. However, as the INR value increased beyond 3.5, the differences of INR values become higher as most of the values fall out of 95% CI. Details on agreement by Bland-Altman analysis are shown in Figure 3.

Figure 3: Bland-Altman analysis between POC and laboratory instrument
4.0 Discussion

Our study demonstrated statistically significant difference between mean INR reading between POC and standard laboratory method (p<0.001). This finding is in line to finding of a study done by Ryan et al. (2008), where the statistically significance differences occur especially at INR values above 3.5 (p < 0.05). It is important to consider whether these differences in INRs, while being statistically significant in many cases, are in fact clinically significant. For example, a difference of 0.9 INR units (e.g. Laboratory INR = 2.0; POC INR = 2.9; INR target range 2.0–3.0) would be statistically significant but the clinical management of the patient would probably not differ. Conversely a difference of 0.6 INR units, (e.g. Laboratory INR = 2.8; POC INR = 3.4; INR target range 2.0–3.0) while not statistically significant, could be clinically important as a different dose may be prescribed depending on which INR is interpreted (Ryan et al., 2008). It is estimated that up to 54% of dosing decisions may be made differently depending on the method of testing (Delaney et al., 1999).

However, in a study by Gardiner et al. (2005), where eighty-four patients consist of 53 men and 31 women who received long-term oral anticoagulant (warfarin), showed no significant differences between the CoaguChek® (median INR 3.02) and laboratory testing (median INR 3.07).

Same goes with a local study done by Chong et al. (2007), the mean difference between INR obtained from standard laboratory method and point of care device was not statistically significant (p=0.935). One interesting observation is that the differences between these two measurements are larger when the INR reading is high. This is not unexpected because conventional INR measuring is most accurate between readings of 1.5 to 4.5. This is due to the fact that WHO calibration model only using plasma from patients within this interval. Therefore, the assigned International Sensitivity Index value that enables the conversion of PT to INR is valid only for this range. As a result, INR at higher value should be interpreted with caution in both methods (Chong et al., 2007).

This study showed strong positive correlation between INR value obtained by POC and standard laboratory which was statistically significant (r= 0.941, p<0.001). This finding is in parallel with a local study done by Chong et al. (2007) in which they found a strong correlation coefficient of 0.967 between capillary and venous INR values among patients. A study in India also reported excellent correlation (r = 0.94) was observed between INR values obtained by CoaguChek® XS and the values obtained in the laboratory by standard laboratory method (Lakshmy & Kumar, 2010).

Apart from that, study from Switzerland which involved one hundred and fifty-five patients in a prospective open comparison study found a strong positive correlation coefficient of 0.85 between capillary and venous INR values (Khoschnewis et al., 2004). Meanwhile, a study in Australia evaluated two POC devices, CoaguChek® and CoaguChek® XS, and showed that the INR values obtained with CoaguChek® XS correlated excellently with laboratory results (Sobieraj-Teague et al., 2009).

In another study in Australia also reported that INR determined by CoaguChek® XS correlated with laboratory determination of INR even in the hands of patients and values compared well with expanded and narrow clinical agreement criteria (Bereznicki et al., 2007).
Despite of only having strong correlation which is 0.9052, study by Dorfman et al. (2005) also found that the POC measurements of INR exhibit positive bias as INR values increase.

Finding from our study also revealed that there was a good agreement and consistency between both methods when INR value less than 3.5. But, as INR increased more than 3.5, the differences of INR values become higher as most of the values fall out of 95% CI. According to Lakshmy and Kumar (2010), a good correlation was seen with correlation coefficient (r) of 0.94 and Intra Class Coefficient of 0.922 between both methods. It is also confirmed with Bland Altman plots which showed good agreement between values obtained by the two methods.

Besides that, another study done in Sabah state, Malaysia also illustrated good overall agreement between the standard laboratory method and CoaguChek® XS. However, they found discrepancies when the INR value went beyond 3.5. This study reveals that the INRs generated by CoaguChek® XS and laboratory are closely correlated and consistent with each other but as INRs increase above 3.5, the disagreement also increases (Shim et al., 2011).

There are many confounding variables that can affect the INR result, hence it would be wrong to assume that the laboratory INR as the true INR value. Inappropriate calibration of instruments, inappropriately assigned ISI values and variability in operator technique can invalidate laboratory INR readings. Besides that, delays in obtaining the blood sample can lower the INR; underfilling the collection tubes would decrease the blood:anticoagulant ratio and prolongs prothrombin time; overfilling can cause cloting. Inappropriate mixing of the sample with the anticoagulant in the tube would activate clotting prior to analysis (Reneke et al., 1998).

False reading can also be caused by POC device. Falsely elevated readings may occur if there is a delay of longer than 15 seconds between lancing the finger and applying the blood to the test strip. Soap and alcohol residues on the finger can also cause higher results. Excessive squeezing of the finger may force tissue clotting factors into the blood sample, accelerating the clotting process and giving a falsely low reading. The portable capillary whole blood coagulation monitor is an alternative to laboratory venipuncture which minimize the possibility of technical error (Ryan et al., 2008).

5.0 Conclusion

In conclusion, the mean differences of INR values between these two methods was statistically significant, but was not clinically significant (mean difference = 0.32). There was a strong correlation and good agreement between INR values obtained from these two methods. However, the disagreement increases when INR values is more than 3.5. Precaution should be practiced by the clinicians or healthcare providers when it comes to clinical judgement. Using the POC device as an alternative to laboratory venipuncture enables us to give more efficient service and frequent INR monitoring which will lead to more patients achieving the INR target range. Due to good correlation and agreement between CoaguChek XS® INR reading and laboratory INR reading, we may conclude that CoaguChek® XS is suitable for outpatient INR monitoring when starting warfarin.
Acknowledgement

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Declaration

The authors declare that this manuscript has never been published in any other journal.

Authors contribution

Author 1: information gathering and manuscript drafting
Author 2: editing and review of manuscript

References


