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Correction of Point-of-Care INR Results in Warfarin Patients

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Abstract

BACKGROUND—The measurement of international normalization ratio (INR) may be done by venous blood draw and use of a standard lab, or by fingerstick, using a point of care (POC) device such as the CoaguChek XS[®] (Roche Diagnostics), and the CoaguChek XS[®] has been validated to meet the International Organization for Standardization (ISO) performance requirements.

OVERVIEW—The goal of this study was to determine a correction factor for CoaguChek XS INR levels to a predicted venipuncture (VP) INR level.

METHODS—At the end of an anticoagulation clinic visit when a patient had an INR greater than or equal to 4, two INR results existed, that from the CoaguChek XS[®] meter and a venipuncture INR from the lab. The data were then discreetly recorded as a quality control for our clinic. The data were analyzed for possible significant trends between the two types of INR results.

RESULTS—The equation that was determined to be the best fit to the data was $0.621 \times \text{POC} + 0.639 = \text{estimated VP}$. The overall root mean square error (MSE) for the calculated correction was a 0.44 INR. The root mean square errors were 0.41 and 0.58 for the 4 to 5.9 and 6 to 7.9 POC INR groups, respectively.

CONCLUSION—The calculation that was derived in this study is not a surrogate for venipuncture INR in this clinic. However, the estimation of the INR may be useful clinically in guiding decision making in the future. (INR, Point of Care, Anticoagulation, Hematology)

Introduction

Warfarin is the most commonly used form of oral anticoagulation for the treatment and long-term prevention of thromboembolic events.¹ Although highly effective, warfarin is a challenge to use in clinical practice because of its narrow therapeutic window, complex pharmacokinetics, variability in dose response between patients, and numerous drug and food interactions. To ensure safe and effective anticoagulation with warfarin therapy, the

maintenance of international normalized ratio (INR) levels within appropriate target ranges is required.

The measurement of international normalization ratio (INR) may be done by venous blood draw and use of a standard lab, or by fingerstick, using a point of care device such as the CoaguChek XS[®] (Roche Diagnostics, Indianapolis, IN, USA). Point of care (POC) devices are more convenient and allow for in-clinic or at home monitoring. However, clinicians and patients must be confident in the accuracy of point of care devices as inaccurate results could have significant implications. The CoaguChek XS[®] has been validated to meet the International Organization for Standardization (ISO) performance requirements.² This standard requires that more than 90% of INR values in the 2.0-4.5 range be within $\pm 30\%$ of the reference lab value.² The ISO requirements do not set standards for INR values above 4.5.² However, some studies have shown that correlation between the CoaguChek XS[®] and standard lab drops significantly with INR values above 3.³⁻⁴ If the CoaguChek XS[®] is inaccurate at higher INR values then a venous draw and standard lab INR must be done to make appropriate patient care decisions. In the anticoagulation clinic at the University of Florida (UF) Health Cardiovascular Center, a venous draw is performed on any CoaguChek XS[®] INR values >4 . This step increases patient cost, wait time and can strain our available resources. Thus, the clinicians began tracking the CoaguChek XS[®] INR values and the standard lab INR values to determine if there was a relationship between the two such that they could estimate the true lab INR value based on the CoaguChek XS[®] value.

The anticoagulation clinic at the UF Health Cardiovascular Center is attended by a hematologist and run by pharmacists. Pharmacy students also see patients that follow-up with our clinic. The circulating census of the clinic is approximately 180 patients, and we see on average approximately 38-42 patients on clinic day. Our clinic is open one day a week for this service. The laboratory at this facility uses a Stago[®] Compact Analyzer with Neoplastin as a reagent (Diagnostica Stago Inc., Parsippany, NJ, USA) for determining the prothrombin time and INR.

The goal of this study was to determine a correction factor for CoaguChek XS[®] INR levels to a predicted venipuncture INR level. The intended use of this factor was to streamline the clinic flow in a trust but verify method, use the correction factor to manage the patient, but obtain a venipuncture INR to verify the correction factor and follow-up if needed after the clinic appointment has completed. This correction factor would be a guide for other institutions to evaluate similar trends as, historically, lab INR values have varied from site to site using different assays⁵.

Methods

At the end of an anticoagulation clinic visit when a patient had an INR greater than or equal to 4, two INR results existed, that from the CoaguChek XS[®] meter and a venipuncture INR from the lab. The data was then discreetly recorded as quality control for our clinic. The data was analyzed for possible significant trends between the two types of INR results. 3 models were analyzed as possible fits for the data, linear, logarithmic, and exponential.

Results

A total of 151 pairs of data were collected between July 19, 2013 and March 19, 2015. 118 of the pairs were between an INR of 4 to 5.9 on the Coaguchek XS[®], and 33 pairs were between 6 and 7.9. The most accurate and consistent model was a simple linear model. This model showed the ability to possibly extrapolate to an INR of 1 and was relatively accurate from the INR range of 4 to 7.9 compared to the other models. The logarithmic model was accurate by comparison at INR values greater than 4 but was not functional below 3 preventing any possible extrapolation. The exponential model was quite similar to the linear model for INR values below 6 but became less accurate above 6. The equation that was determined to be the best fit to the data was $0.621 \times \text{POC} + 0.639 = \text{predicted venipuncture}$.

The first analysis of the results performed was a regression analysis using the variable Coaguchek XS[®](CXS) and observations from venipuncture, and *proc reg* from SAS[®] (SAS Institute Inc., Cary, NC, USA) was used for running this regression model followed by the SAS[®] output. After reviewing this output carefully, the F-test was statistically significant, which means that the model was statistically significant, and the R-squared value, 0.673, means that approximately 2/3 of the variance of venipuncture was accounted for CXS by the model. The root mean square error was 0.44, and the t-test for CXS, which was the observations from lab, equals 17.5 and was statistically significant meaning that the regression coefficient for CXS was significantly different from zero ($p < 0.0001$). Figure 1 shows a scatterplot of the predicted and outcome variables where x is the CXS result and y is the venipuncture result.

Next analysis focused on regression diagnostics to verify whether the data met the assumptions of linear regression. Firstly, the residuals needed to be normally distributed, and its variance was constant. Figure 2 plotted a residual versus fitted plot. The variance of residuals is shown to be constant. To see the distribution of residuals, figure 3 shows the histogram of residuals with the kernel density plot and normal density plot, and figure 4 draws a normal probability plot for examining the distribution of residuals. From both plots, analysis indicated normality in residuals.

After examine the data, it was found that more data are concentrated for $x < 6$. After fitting the pure error model for the raw data in the 4 to 5.9 group, the root mean square error on pure error is 0.41 which was slightly smaller than the root mean square error when fitting the linear model (0.44). This means the investigators were about 70% confident that the fitted value by CXS was within 0.41 units of venipuncture and 95% confident that the fitted value by CXS was within 0.8 units of venipuncture. In the 6 to 7.9 group, it was found that the root mean square error was 0.58 meaning the investigators were about 70% confident that the fitted value by CXS was within 0.58 units of venipuncture and 95% confident that the fitted value by CXS was within 1.2 units of venipuncture.

Discussion

While the equation is not a surrogate model for the venipuncture verification of the INR, several questions arise regarding the data. First, while the venipuncture INR is the gold

standard by which clinical decisions are made for patients on warfarin, the lab can give inaccurate results. Lab error has been documented to be a concern in anticoagulation clinics especially in the pre-analytical period after drawing a blood sample⁶. Even in this specific period, error rates are typically less than 10% of all samples. However, in the UF Health anticoagulation clinic during the time of the study, extended periods of time from the drawing of the sample until analysis were observed that were up to 1.5 hours when patients required venipuncture verification. This was not recorded as part of the study, but it is unknown how much impact this would have on the variability of the results.

Since the estimation is not a good surrogate for a venipuncture INR, use of this estimation equation in clinical practice would only be warranted as a guide to streamline clinic flow. A trust but verify method may be a good model wherein the patient has a venipuncture INR after leaving clinic to validate decisions made to manage the patient's warfarin dosing. In order to be able to use this equation as a sole clinical tool for managing a patient's warfarin therapy, research must be done comparing clinical decisions using this estimation equation with the venipuncture INR.

Another concern regarding the estimation equation is the ability to use the equation on POC INR values less than 4. Since the study did not assess INR values less than 4, no legitimate claims can be made regarding these calculations, but the linear model of the estimation does appear to be extrapolated nearly to an INR of 1. For example, an INR of 3.8 on the POC test would result in an estimated correction value of 3, and a 3 on the POC test would result in a value of 2.5. In INR values less than 2.8, extrapolation of the estimation equation become much less relevant since the standard error begins to include the original POC INR value. Clinically, a single INR value up to 3.3 for a patient historically within a therapeutic range of 2-3 would not warrant change, but if the INR value was found to be 3.8, a different clinical decision would presumably be made compared to an estimated venipuncture of 3.

The reagent used by the laboratory for this clinic, Neoplastin, is one of several reagents used to measure INR. A study by Samama et al. compared several reagents in an evaluation of the effects of rivaroxaban on INR, and recorded a great deal of variability among these reagents⁵. For example an INR of 3 using Recombiplastin (Instrumental Laboratory, Bedford, MA, USA) correlated with INRs of 2.4 and 1.4 with Neoplastin and Innovin (Siemens Healthcare Diagnostics Inc., Newark, DE, USA), respectively. While the study by Samama et al. assessed the effect of rivaroxaban and not warfarin on these assays, this still demonstrates the variability possible between assays. The comparison of the CXS INR to the UF Health laboratory result is limited to the Neoplastin reagent, and would not have the same correlation with other reagents used in other institutions.

Over the course of this study three lots of Neoplastin reagent were used by the laboratory at UF Health. The protocol for the laboratory dictates that lots are changed every September. This gives some credibility to the study in regard to concerns over variability between lots of reagent. Also, as the study did not initially track the lot numbers of the CoaguChek XS[®] test strips, the lot numbers could not be obtained retrospectively from the distributor.

The calculation that was derived in this study is not a surrogate for venipuncture INR in our clinic. However, the estimation of the INR may be useful clinically in guiding decision making in the future. Further investigation needs to be done to evaluate if decisions made using this estimation are clinically different than decisions made using a follow-up venipuncture INR after obtaining an INR greater than 4 on the Coaguchek XS®.

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Figure 1.
Scatter plot of predicted and outcome variables where x is the Coaguchek XS[®] result and y is the venipuncture result.

Figure 2.

A residual versus fitted plot. The variance of residuals is shown to be constant. The equation above the plot is the estimation equation where x is the Coaguchek XS[®] result and y is the estimated venipuncture INR.

Figure 3.
The histogram of residuals with the kernel density plot and normal density plot.

Figure 4.
A normal probability plot for examining the distribution of residuals.