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Use of error grid analysis to evaluate acceptability of a point of care prothrombin time meter

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ABSTRACT

Background: Statistical methods (linear regression, correlation analysis, etc.) are frequently employed in comparing methods in the central laboratory (CL). Assessing acceptability of point of care testing (POCT) equipment, however, is more difficult because statistically significant biases may not have an impact on clinical care. We showed how error grid (EG) analysis can be used to evaluate POCT PT INR with the CL.
Materials and methods: We compared results from 103 patients seen in an anti-coagulation clinic that were on Coumadin maintenance therapy using fingerstick samples for POCT (Roche CoaguChek XS and S) and citrated venous blood samples for CL (Stago STAR). To compare clinical acceptability of results we developed an EG with zones A, B, C and D.
Results: Using 2nd order polynomial equation analysis, POCT results highly correlate with the CL for CoaguChek XS ($R^2 = 0.955$) and CoaguChek S ($R^2 = 0.93$), respectively but does not indicate if POCT results are clinically interchangeable with the CL. Using EG it is readily apparent which levels can be considered clinically identical to the CL despite analytical bias.
Conclusion: We have demonstrated the usefulness of EG in determining acceptability of POCT PT INR testing and how it can be used to determine cut-offs where differences in POCT results may impact clinical care.

1. Introduction

Treatment of patients with oral anticoagulants, such as warfarin or Coumadin, is necessary to prevent thromboembolic events in the treatment of a number of clinical conditions [1]. However, the therapeutic effect of a dose of Coumadin given to a patient can be highly variable depending upon genetics, diet, and medications prescribed for other co-morbid conditions. According to the most recent recommendations of the American College of Chest Physicians, changes in warfarin dosage depend on 2 factors: INR values and the presence of bleeding [2]. Thus, regular monitoring of the prothrombin time (PT) international normalized ratio (INR) is necessary to minimize both the complications of bleeding and thromboembolic events if the PT INR is not kept within a narrow therapeutic range. A number of studies involving patient self monitoring and point of care (POCT) testing have shown positive patient outcomes with patients more often in the therapeutic range [3–7] while other studies have questioned the accuracy of POCT PT INR meters [8–10]. Although POCT PT INR has been shown to be useful, the results should be comparable to the central laboratory, at least in the therapeutic range (PT INR <4.0). Determining the acceptability of a new method usually depends upon simple statistical tools, such as Bland Altman plots, linear regression, and correlation analysis. While use of these methods is adequate when performing method comparison in the clinical laboratory (CL); using them to determine the clinical acceptability of POCT meters is often more difficult. This is because statistically significant analytical biases may not alter the clinical impression and thus have no impact on clinical care. Change in warfarin dosage is a clinical decision, which among other factors depends on the patient's underlying medical condition. Anderson et al. attempted to deal with these differences by developing additional criteria that tried to account for the clinical impression along with analytical biases [11]. While useful, their criteria requires detailed analysis and may not be stringent enough, especially when the PT INR is <3.0. Another method that is useful in comparing POCT to the CL is error grid (EG) analysis. While developed to determine acceptability of POCT glucose meters [12,13] EG analysis has not been used routinely in the evaluation of other POCT tests. The only exception is a recent study in which EG analysis was used to evaluate the acceptability of two PT INR meters for patient self monitoring [14].

During our evaluation of the CoaguCheck XS (Roche Diagnostics, Indianapolis, IN) as a potential replacement for the CoaguCheck S (Roche) we had the opportunity to use EG analysis to compare the results of the POCT meters with the results obtained from the CL (Stago STAR, Parsippany, NJ).

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2. Materials and methods

2.1. PT INR measurements

Central laboratory analysis was performed on a Stago STAR (Stago, ISI = 1.29) using 3.2% citrated platelet-poor plasma. Samples were processed and analyzed within 8 h of collection. The CoaguChek S® (Roche) device used recombinant thromboplastin (ISI = 1.0) with clot formation detected by iron particles that are moved by an alternating electrical field. The CoaguChek XS (Roche Diagnostics, Indianapolis, IN) device used recombinant thromboplastin (ISI = 1.0) and employs electrochemical current detection to measure clot formation.

2.2. Study participants

The study was approved by the University of Texas Medical Branch (UTMB) Institutional Review Board and conducted in the anti-coagulation and outpatient clinics at UTMB. The clinics have a high volume of patients that are routinely evaluated for long term anti-coagulation therapy. Patients were included in the study (103 for Stago STAR, 99 for CoaguChek XS and 64 for CoaguChek S) as they presented to the clinic and gave permission that in addition to a finger stick they were also willing to have drawn a tube of blood (3.2% Sodium citrate) that was sent to the main Hematology laboratory for PT INR analysis. Patients that were not on Coumadin therapy (20 for Stago STAR and CoaguChek XS and 14 for CoaguChek S) were considered normal and were included in the study if they gave permission to have a finger stick and to have drawn a tube of citrated blood that was sent to the main Hematology laboratory for analysis. Blood for analysis in the central laboratory was drawn within 15 min of finger stick analysis. No patients were excluded from the study due to extremely high PT-INR.

2.3. Statistical analysis

The EG was developed in conjunction with a Hematopathologist (MTE) and an Internal Medicine physician (HMV) with expertise in anti-coagulation therapy. The EG that was developed was based entirely on expert opinion and has had no performance-based validation. Using the EG that had been developed to evaluate POCT blood glucose monitors as the model [7,8] the following EG zones developed:

Zone A - Results that may not be identical but the difference between the methods (defined as Clinical Laboratory PT-INR ± 15%) will have no effect on the required clinical action. In other words the results are clinically identical.

Zone B - The results are substantially different, however, any altered clinical action will have little or no impact on a patient's clinical outcome (defined as Clinical Laboratory PT-INR ± 15–25% for PT INR values <4.0). For example, corrective action, while required, is in the correct direction but will be slightly greater or less than required.

Zone C - The results are substantially different resulting in an altered clinical action that could have a significant medical risk. This could lead to under or over dosing the patient causing a patient to be at risk of bleeding complications (over anti-coagulated) or thromboembolic events (under anti-coagulation).

Zone D - The results are substantially different resulting in altered clinical action possibly having dangerous and life threatening medical risk. The difference between the methods is great enough that severe over or under anti-coagulation has occurred and the patient is at a significantly increased risk of bleeding complications or thromboembolic events.

The statistical differences between the PT INR devices and the CL were assessed by the Wilcoxon rank sum test for paired samples using MedCalc (Mariakerke, Belgium). We also utilized McNemar's test and the κ statistic to measure the degree of agreement between the CL vs. CoaguChek XS® and CoaguChek S®. Specifically, we utilized the mean ± SD PT INR values from CL and dichotomized both the CoaguChek XS® and CoaguChek S® PT INR values as within or beyond the Zone A boundary from the CL data. We also performed power calculations based on the κ statistic.

3. Results

As part of this study, patients had capillary whole blood PT INR determinations using POCT instrumentation (CoaguChek XS and/or CoaguChek S) followed by venous blood sampling for PT INR determination in the CL (Stago STAR). Of the 103 patient samples (20 normal and 83 on Coumadin therapy) sent to the CL for PT INR determination, 99 were tested using the CoaguChek XS meter, 64 were tested using the CoaguChek S meter, and 56 were tested using both POCT meters. The CL PT INR values for the samples ranged from 0.9 to 7.0. Table 1 shows the mean (SD) for CL PT INR ranging from ≤3.0, >3.0–4.0, and >4.0. For a CL PT INR ≤3.0 the mean bias between the CoaguChek S and the CoaguChek XS relative to the CL was 0.06 ($p = 0.63$) and 0.09 ($p = 0.003$) PT INR units, respectively. The differences between the CoaguChek XS and CoaguChek S were not statistically significant ($p > 0.1$), however, the CoaguChek S showed increased variability as compared to the CoaguChek XS relative to the CL values ($S_{y/x} = 0.25$ vs. 0.13, respectively). The same trend is also seen for all PT INR ranges. Although both the CoaguChek XS and CoaguChek S compare reasonably well with the CL when the CL PT INR <3.0, when the CL PT INR is >3.0 overestimation of the CL values is apparent with both meters. Both the increased variability for the CoaguChek S and the overestimation for both meters with increasing PT INR are readily apparent by inspection of the respective EG (Fig. 1A–B). Since the differences between the CoaguChek XS and CoaguChek S appear to be curvilinear the relationship was expressed as a 2nd order polynomial equation: $y = -0.02\ x^2 + 1.40\ x - 0.55$; $R^2 = 0.955$ and $y = 0.15\ x^2 + 0.56\ x + 0.23$; $R^2 = 0.93$ for CoaguChek XS and CoaguChek S, respectively.

In order to better assess the clinical significance of differences between the POCT and CL PT INR results we applied our proposed

Table 1
Mean PT INR for Stago STAR, CoaguChek S, and CoaguChek XS for patients whose PT INR for Stago STAR was ≤3.0, 3.1–4.0, >4.0.

	Stago STAR	Stago STAR	Stago STAR
	PT INR ≤3.0	PT INR >3.0–4.0	PT INR >4.0
Stago STAR			
PT INR (SD)	1.79 (0.64)	3.6 (0.27)	4.8 (0.76)
N	57	22	24
CoaguChek S			
PT INR (SD)	1.85 (0.74)	4.3 (0.81)	5.94 (1.11)
$S_{y/x}$	0.25	0.52	0.95
N	41	13	10
p (Wilcoxon) (vs. Stago STAR)	0.47	0.014	0.002
κ Coefficient	0.66	0.64	Not estimable
H_0: $\kappa = 0$	<0.0001	0.022	
p (McNemar's test of equality of proportions)	NS	NS	
CoaguChek XS			
PT INR (SD)	1.88 (0.70)	4.18 (0.47)	5.92 (0.83)
$S_{y/x}$	0.13	0.31	0.54
N	54	22	23
p (Wilcoxon) (vs. Stago STAR)	0.009	<0.001	<0.001
κ Coefficient	0.82	0.10	0.12
H_0: $\kappa = 0$	<0.0001	0.52	0.22
p (McNemar's test of equality of Proportions)	NS	0.011	0.0003