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Original Article

I-STAT, COAGUCHEK XS PLUS, AND HEMOCHRON VERSUS REFERENCE LABORATORY INRS: PHARMACIST-MANAGED CLINICS

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ABSTRACT

Objectives: The international normalized ratio (INR) is the primary measure used to determine the therapeutic effect of warfarin. I-Stat, CoaguChek-XS Plus, and Hemochron are the most frequently used point-of-care tests (POCTs); hence, we compared the results of each with our reference laboratory results.

Methods: Subjects were recruited during our clinic's annual evaluation phase for therapeutic optimization. Upon acceptance, an instant finger-stick or finger-prick test was performed as required in addition to venous blood sampling. Approximately 0.1–0.3 mL of blood was taken peripherally for the POCTs, whereas 3 mL was taken for the reference laboratory to measure the INR. Bland-Altman plots were used to analyze the data and test their agreement.

Results: A total of 180 blood samples were taken from 45 patients. The sample volumes for Hemochron were higher than for I-Stat and CoaguChek-XS Plus, and 70% of patients reported more pain for this method. While I-Stat has additional test options and does not require a finger stick, CoaguChek-XS Plus is the cheapest test in terms of the acquisition cost for the handset and strips. The INR estimated by the reference laboratory ranged from 1.1 to 8. The Bland-Altman plots revealed a good agreement between methods, with only 3–6 outliers in each plot. Of the samples, 6%, 6%, and 13% of the results were considered to be outside the clinically acceptable range (±0.5 INR) for I-Stat, CoaguChek-XS Plus, and Hemochron, respectively.

Conclusion: The results obtained using the three POCTs are in good agreement with the reference laboratory results.

Keywords: I-Stat, CoaguChek-XS Plus, Hemochron, Warfarin.

INTRODUCTION

Warfarin is the cornerstone of the treatment of many thrombotic disorders worldwide, despite the availability of new oral anticoagulants [1]. Many patients on warfarin require tedious monitoring, and their international normal ratios (INRs) should be kept within the therapeutic range for as long as possible to minimize potential thrombotic or bleeding events [2]. Many INR clinics worldwide use point-of-care testing (POCT) handsets to improve patient compliance and enhance the flow at the facility. It is thought that POCT handsets are underused for several reasons, including physician, patient, and community factors [3]. Furthermore, POCT is proven to prolong the time in the therapeutic range (TTR) and reduce strokes compared to routine monitoring [1,3]. The handsets are also a less invasive option for the patient and can be used by the clinic pharmacist or onsite physician.

However, the availability of various handsets has made the choice difficult [4-8]. Roche produces the mostly commonly used handsets, which have been studied extensively [8-17]. The variety of handsets available has also contributed to the avoidance of such technology. Because assays vary significantly among handsets, the agreement of reported INR values in the published literature has varied for the handsets. [4-17]. Furthermore, there is great variation in the statistical methodology, which may have contributed to the variation in reported results. Nonetheless, most INR clinics operate at full capacity, and finding an easy and fast method for obtaining results is important. This study aimed to compare I-Stat, Coagu Chek XS Plus, and Hemochron against the reference laboratory results to determine the best handset for anticoagulation clinical use.

MATERIALS AND METHODS

Subjects were recruited as a part of a regular evaluation phase at the clinic, which is conducted annually for the purpose of therapeutic optimization. The experimental study was conducted in the Prince Sultan Cardiac Center in Buriadah, Saudi Arabia. Ethical approval was obtained from the Ethical Committee at King Fahad Specialist Hospital prior to conducting the experiment. Informed consent was obtained from the patients prior to the study. Upon acceptance, an instant finger-stick or finger-prick test was performed as required, in addition to venous blood sampling. Approximately 0.1–0.3 mL of blood per sample was taken peripherally, and 3 mL was taken for the reference laboratory (Cobas 6000, Roche Diagnostics, Indianapolis, IN, USA) to perform the INR test. Blood samples were obtained from patients visiting the INR clinic for routine warfarin monitoring using I-Stat (Abbott Laboratories, Abbott Park, IL, USA), Coagu Chek-XS plus (Roche Diagnostics), and Hemochron (International Technidyne Corporation, Edison, NJ, USA) for each patient. The finger-prick method was used for patients being tested with Hemochron because the handset requires roughly three drops of blood and a simple finger -stick may only produce one or two drops.

All data were stored in MedCalc® for analysis. The sample size used to detect statistically significant differences was 40 patients (160 units). $P < 0.05$ was considered statistically significant A Bland-Altman plot was used to analyze the data and test for agreement among the methods [18]. Furthermore, receiver operating characteristic curves (ROCs) with sensitivity and specificity were plotted and compared.

RESULTS

A total of 180 blood samples were taken from 45 patients with a mean age of 60 (SD ± 10) years and a mean body mass index of 29 (SD ± 3) (Table 1). Two patients were excluded from the analysis due to errors in all three handsets.

The sample volumes taken for Hemochron were higher than for I-Stat and Coagu Chek-XS Plus, and 70% of the patients reported more pain for this method. The INR reported by the reference laboratory ranged from 1.1 to 8, and 95% of the values were between 1 and 4. Bland-Altman plots generally revealed good agreement between methods; only 3–6 outliers were present in each plot (Figs. 1–3). Of the samples, 6%, 6%, and 13% were considered to be outside the

clinically acceptable range (±0.5 INR) for I-Stat, Coagu Chek-XS Plus, and Hemochron, respectively.

Table 1: Patient demographics

Demographics	Percentage (%)
Males	75%
Females	25%
Diabetes Mellitus	76%
Hypertension	63.24%
Atrial Fibrillation	100%

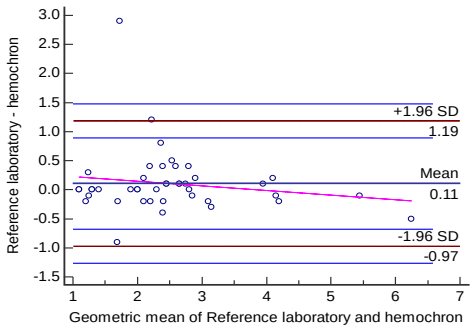

Fig. 1: Bland-Altman plot for the reference laboratory versus Hemochron®

Table 2: Analysis of the reference laboratory versus Hemochron results

Statistics	Result
Arithmetic mean	0.1070
95% CI	-0.06284 to 0.2768
P (H_0:Mean = 0)	0.2106
Standard deviation	0.5518
Lower limit	-0.9745
95% CI	-1.2670 to-0.6820
Upper limit	1.1885
95% CI	0.8960 to 1.4810

The difference between the INR estimated by the reference laboratory and Hemochron was very small (0.1070 ± 0.5518; P = 0.2106), indicating that there was not a significant difference between these methods. Based on a visual inspection of the plot, the results obtained using the two methods were not identical, but they were within an acceptable range with respect to their agreement. There were a few outlier INR data points that were not clinically acceptable.

Table 3: Hemochron results versus those of the main laboratory

Reference laboratory	Hemochron	Difference
1.1	1.1	0
1.1	1.1	0
1.1	1.3	-0.2
1.2	1.3	-0.1
1.3	1.3	0
1.3	1.3	0
1.3	2.2	-0.9
1.3	1.3	0
1.4	1.4	0
1.4	1.1	0.3
1.6	1.8	-0.2
1.9	1.9	0
2	2.2	-0.2
2	2	0
2	2	0
2.1	2.3	-0.2
2.2	2	0.2
2.2	2.6	-0.4
2.3	2.3	0
2.3	2.5	-0.2
2.4	2	0.4
2.5	2.4	0.1
2.5	2.4	0.1
2.6	2.2	0.4
2.7	2.6	0.1
2.7	2.6	0.1
2.8	2	0.8
2.8	2.2	0.6
2.8	2.4	0.4
2.8	2.8	0
2.8	2.7	0.1
2.8	2.9	-0.1
2.9	1.7	1.2
3	2.8	0.2
3	2.4	0.6
3	3.2	-0.2
3	3.3	-0.3
3.7	0.8	2.9
4	3.9	0.1
4.1	4.3	-0.2
4.1	4.2	-0.1
4.2	4	0.2
5.4	5.5	-0.1
6	6.5	-0.5
8	>8	--

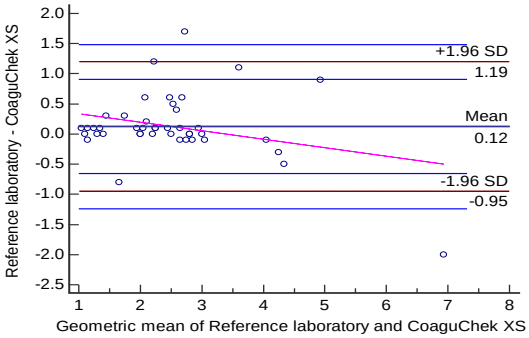

Fig. 2: Bland-Altman plot for the reference laboratory versus CoaguChek-XS Plus

Table 4: Analysis of the results from the reference laboratory versus CoaguChek-XS Plus

Statistics	Result
Arithmetic mean	0.1233
95% CI	-0.04502 to 0.2915
P (H_0:Mean = 0)	0.1468
Standard deviation	0.5468
Lower limit	-0.9484
95% CI	-1.2383 to-0.6586
Upper limit	1.1949
95% CI	0.9051 to 1.4848

The difference between the INR estimated by the reference laboratory and CoaguChek-XS Plus (0.1233 ± 0.5468) was slightly higher than the difference between the reference laboratory and Hemochron results, and was not statistically significant (P = 0.1468).

The results obtained using the two methods were not identical, but they agreed within an acceptable range. Again, there were outlier INR values, which were not clinically acceptable.

Table 5: Coagu Chek-XS Plus results versus those of the main laboratory

Reference laboratory	Coagu Chek-XS Plus	Difference
1.1	1.1	0
1.1	1	0.1
1.1	1.2	-0.1
1.2	1.1	0.1
1.3	1.3	0
1.3	1.2	0.1
1.3	2.1	-0.8
1.3	1.3	0
1.4	1.4	0
1.4	1.3	0.1
1.6	1.3	0.3
1.9	1.6	0.3
2	2	0
2	1.9	0.1
2	2	0
2.1	2	0.1
2.2	2	0.2
2.2	2.2	0
2.3	2.2	0.1
2.3	2.2	0.1
2.4	1.9	0.5
2.5	2.4	0.1
2.5	2.5	0
2.6	2.7	-0.1
2.7	2.6	0.1
2.7	2.8	-0.1
2.8	2.9	-0.1
2.8	2.3	0.5
2.8	2.3	0.5
2.8	2.8	0
2.8	2.8	0
2.8	2.4	0.4
2.9	1.7	1.2
3	3	0
3	2.9	0.1
3	3.1	-0.1
3	2.6	0.4
3.7	2	1.7
4	4.1	-0.1
4.1	4.6	-0.5
4.1	4.4	-0.3
4.2	3.1	1.1
5.4	4.5	0.9
6	8	-2
8	>8	--

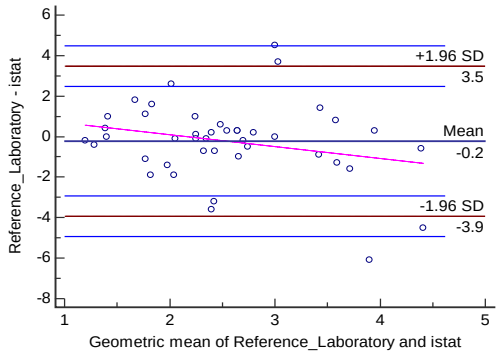

Fig. 3: Bland-Altman plot for the reference laboratory versus I-Stat®

The difference between the INR estimated by the reference laboratory and I-Stat (0.2302 ± 1.8896) was higher than the difference between the INR estimated by the reference laboratory and either Hemochron or CoaguChek-XS Plus, and the difference was not statistically significant (P = 0.4288). Although the SD was higher than it was for the comparisons using the other methods, the agreement was within an acceptable range. Further, the same outlier INRs existed (i. e., INRs of samples from the same patients).

Table 6: Analysis of the reference laboratory versus I-Stat results

Statistics	Result
Arithmetic mean	-0.2302
95% CI	-0.8118 to 0.3513
P (H_0:Mean = 0)	0.4288
Standard deviation	1.8896
Lower limit	-3.9339
95% CI	-4.9356 to-2.9323
Upper limit	3.4735
95% CI	2.4718 to 4.4751

Table 7: I-Stat results versus those of the main laboratory

Reference laboratory	I-Stat	Difference
1.1	1	0.1
1.1	1.1	0
1.1	1	0.1
1.2	1.3	-0.1
1.3	1.2	0.1
1.3	1	0.3
1.3	1.1	0.2
1.3	1.3	0
1.4	1.3	0.1
1.4	1.3	0.1
1.6	1.6	0
1.9	1.7	0.2
2	1.8	0.2
2	2	0
2	1.9	0.1
2.1	2.2	-0.1
2.2	2.4	-0.2
2.2	2.4	-0.2
2.3	2.1	0.2
2.3	2.5	-0.2
2.4	2.4	0
2.5	2.4	0.1
2.5	2.3	0.2
2.6	2.3	0.3
2.7	2.7	0
2.7	2.8	-0.1
2.8	2.8	0
2.8	3	-0.2
2.8	2.7	0.1
2.8	2.7	0.1
2.8	2.8	0
2.8	2.9	-0.1
2.9	2	0.9
3	3	0
3	3.1	-0.1
3	3	0
3	2.8	0.2
3.7	1.9	1.8
4	4.2	-0.2
4.1	3.8	0.3
4.1	3.9	0.2
4.2	4.6	-0.4
5.4	4.8	0.6
6	4.3	1.7
8	8	0

DISCUSSION

The availability of various INR handsets has encouraged researchers to investigate their accuracy for clinical application. The most

studied handset is the CoaguChek-XS Plus, but there are large discrepancies in the results and methodologies of these studies. However, the results of most studies are in good agreement and emphasize a systematic and frequent quality assurance system [8-15]. This study revealed that I-Stat, CoaguChek-XS Plus, and Hemochron can each be used at INR clinics with an acceptable agreement with the reference laboratory INR estimates. However, Hemochron had slightly more clinically unacceptable readings than I-Stat and CoaguChek-XS Plus, though the difference was not statistically significant.

Figs. 4–6 ROC show that the three handsets have acceptable clinical utilization with some degree of variability among them. table 4 showed the differences in specificity and sensitivity when high INR values were included.

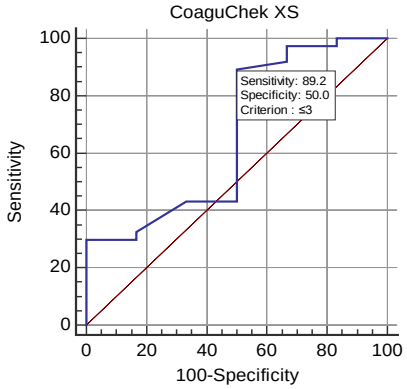

Fig. 4: ROC for I-Stat

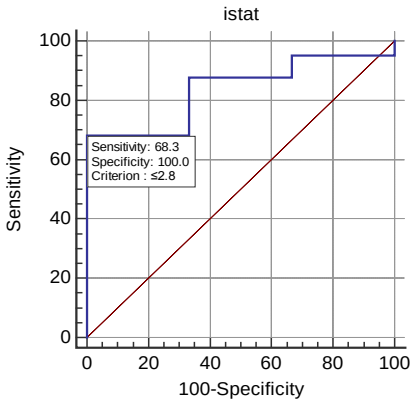

Fig. 5: ROC for Coagu Chek-XS Plus

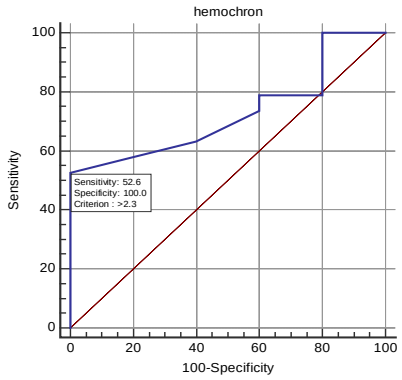

Fig. 6: ROC for Hemochron

Table 8: Comparison between sensitivity and specificity

	Sensitivity % (INR 1–8)	Sensitivity % (INR 1–4)	Specificity % (INR 1–8)	Specificity % (INR 1–4)
Hemochro ®	52	60	100	100
I-Stat®	68	90	100	100
CoaguChek -XS Plus®	89	60	50	100

Other studies have also suggested that using Hemochron requires a higher quality system to ensure a good clinical agreement, and some advised against its routine use because of this weak agreement [19-21]. In contrast, studies that investigated I-Stat tend to recommend it for clinical use and advocate its precision and agreement [22-24]. The reference laboratories varied among studies, which may make an informed decision difficult. Interestingly, the patients that presented outlier INR values showed errors when using all the handsets, but were not tested for any potential antibodies. Several studies have suggested the potential impact of anti phospholipid antibodies on INR results, especially for POCTs, and erroneous INRs may be estimated [7]. Detection in these types of patients is challenging, and they can be at serious thrombotic or bleeding risk. Test results may influence the clinical decision if the reported result was ±0.5 INR. Of the samples, 6%, 6%, and 13% were considered to be outside the clinically acceptable range (±0.5 INR) for I-Stat, CoaguChek-XS Plus, and Hemochron, respectively. However, we did not report any thrombotic or bleeding events. Thus, considering the agreement among individuals may facilitate the best clinical outcomes. Based on the ROC curves, the sensitivity and specificity improved significantly when high INR values were excluded. Furthermore, sample size of high INR values was inadequate. Thus, further evaluation for high INR readings is required before determining an implementation plan.

Another issue is that Hemochron requires roughly three blood drops, necessitating a relatively painful finger prick, whereas just one drop is required for I-Stat and CoaguChek-XS Plus. Most of the patients were elderly and had some degree of claudication, making blood draws difficult and painful. I-Stat takes the longest time to produce results, at about 2 minutes, whereas CoaguChek-XS Plus is the fastest method, showing results in 30 seconds. Thus, I-Stat might not be preferable in a particularly busy clinic. However, I-Stat has some additional test options, such as testing through venous blood, and includes creatinine, hemoglobin, potassium, sodium, and other assays, making it attractive for some clinicians.

At our clinic, CoaguChek-XS Plus is considered the cheapest test in terms of the acquisition cost for the handset and strips, and I-Stat and Hemochron are comparable in this respect. However, the price may vary significantly among countries and settings, depending on the condition of the required handset. One limitation of this study is that most of the patients were in the INR range of 1–4; therefore, the results of the study should not be extrapolated to higher readings. Furthermore, a larger sample size may be required to confirm the results.

CONCLUSION

I-Stat, CoaguChek-XS plus, and Hemochron can be used at INR clinics, as they showed relatively good agreement with the main reference laboratory for INR values in the range of 1–4. Testing the agreement for each individual during initiation may be of value. Should the readings increase over time, it is judicious to confirm the results with the reference laboratory.

CONFLICT OF INTERESTS

Declared None

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