Comparative Study of a Portable System for Prothrombin Monitoring Using Capillary Blood against Venous Blood Measurements in Patients Using Oral Anticoagulants: Correlation and Concordance

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Summary

Background: Oral anticoagulants (OAC) are widely used in cardiology and are mainly indicated in cases of atrial fibrillation and prosthetic heart valves. Regular prothrombin time (PT) control is required for patients using OAC. New portable monitoring systems for measuring prothrombin time, eliminate the need to collect blood by venous puncture and facilitate daily life for these patients.

Objective: To compare PT measurements using the Coaguchek S™ system with capillary blood and the standard method in venous blood.

Methods: One hundred and twenty-seven patients from the Cardiology Institute's anticoagulation clinic underwent conventional blood collection and capillary blood collection via a finger prick for measurements using the Coaguchek S™ system.

Results: The mean age was 58 ± 14 years and 90% of the patients were white. OAC indications were atrial fibrillation (49.6%) and prosthetic heart valves (37.0%). The correlation coefficient, r_s, was 0.90 (p<0.0001; CI:95% 0.87-0.93) between the Coaguchek S™ system and the control method. The Kappa measure of agreement among the patients with INR <2, INR between 2 and 3.5 and INR > 3.5 was 73.5%. The Coaguchek S™ system overestimated INR by 0.15±0.85 units. A great deal of discrepancy was found between the two techniques for INR values higher than 3.5 units.

Conclusion: The Coaguchek S™ system when compared to the control method revealed good correlation and a high degree of agreement for results lower than 4 units. However, confirmation is required for INR values above 3.5 using the standard method. (Arq Bras Cardiol 2007; 89(1) : 1-5)

Key words: Anticoagulants; prothrombin; coumarins; prothrombin time.

Introduction

The advent of portable monitoring systems to measure prothrombin time has facilitated the treatment of patients who require oral anticoagulant therapy (Vitamin K antagonists, warfarin or phenprocoumon)[1]. These systems do not require venous blood collection as they use capillary blood from a finger prick that is analyzed with a reagent test strip and digital device[2].

This test is very easy to perform and can be conducted anywhere including the patient's home, primary care facilities or hospitals[3,4]. These devices use microfluid technology and various detection methods to generate a prothrombin time measurement eliminating the need to draw peripheral venous blood.

Various prothrombin time control devices are currently available[5]. The Mayo Clinic Thrombophilia Center uses the Coaguchek S™ system (Roche Diagnostics, Indianapolis, Ind., USA) to control patients on anticoagulant medication[6]. Prospective comparisons of these devices with laboratory measurements has never been conducted for actual situations in Brazil.

Control of the anticoagulant effect of vitamin K antagonists is usually performed using venous prothrombin time measurements that require venous puncture, skilled technicians to perform the procedure, transportation time to deliver the sample to the laboratory and biochemical technicians to analyze the sample.

The objective of this study is to compare the Coaguchek S™ prothrombin time monitoring system, with the standard method used at a recognized cardiology hospital on patients undergoing treatment in a specialized anticoagulation outpatient clinic.

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Methods

During April 2006, a cross-sectional study was conducted that involved 127 consecutive patients using oral anticoagulant medication who were undergoing treatment at the outpatient anticoagulation clinic of the *Instituto de Cardiologia do Rio Grande do Sul* (IC/FUC – Cardiology Institute of Rio Grande do Sul), a recognized tertiary cardiology hospital in the southern part of Brazil. This specialized clinic treats approximately 1,200 adult and pediatric patients per month.

The patients underwent venous puncture blood collection for the prothrombin time test at our Institution's clinical analysis laboratory, and at the same time, capillary blood from a finger prick was collected for testing with the Coaguchek S™ system. The samples were recollected in the case of preanalytical errors (unsuccessful finger prick, blood applied incorrectly on the reagent strip).

The Coaguchek S™ point-of-care system is a battery powered laser photometer portable device. To conduct the test, a drop of capillary blood, roughly 10μl, was collected from the patient's index finger. The SoftCLix (Boehringer-Manheim, Germany) lancet device was used for the finger prick. The drop was then placed on a reagent test strip containing thromboplastin and iron particles that mix with the blood. As soon as the blood starts to coagulate, the activity of the ferrous oxide particles diminishes until they are completely immobile. The mobility changes were measured using photometry to determine the prothrombin time.

The conventional method was performed via venous puncture and 10ml of venous blood was collected in a test tube with 3.2% of sodium citrate which, after the collection, was immediately sent to the Institution's central laboratory. The measurement of the venous prothrombin time was conducted in the laboratory using human thromboplastin, Thromborel S™ (Dade Behring, Newark, USA), in a CA-500 automatic system (Sysmex Corporation, Kobe, Japan), with ISI = 1. The recommendations of the World Health Organization were used to prepare the thromboplastin.

Statistical analysis was performed using the computer programs SPSS v. 12 and Medcalc v. 8.2. The continuous data of the plasma and capillary prothrombin time measurements in international normalized ratio (INR) units were analyzed using the Spearman (r_s) coefficient. These venous and capillary prothrombin time measurement data in INR units, were also ranked to analyze the difference between the values obtained and the standard deviation.

The difference between the study methods (bias) was compared using the average of the two measurements and graphical representation as per the Bland-Altman[7] method to demonstrate trends and systematic errors. The limits of agreement between the two techniques were calculated as the difference of the averages ±1.96 standard deviation. The Kappa index was used to evaluate the agreement between patients for categorical variables (INR <2; between 2 and 3.5; and > 3.5)[8].

The estimated sample size to detect a r_s=0.9, with a 5% alpha error and 20% beta error would be 7 measurements for each method; however, according to the authors of the Bland-Altman method, a sample size greater than 100 is indicated[9].

The research protocol was approved by the Research and Ethics Committee of our Hospital and all patients signed an informed consent form to participate in the study.

Results

The characteristics of the study population are shown in table 1. The main indication for oral anticoagulant medication in the study population was atrial fibrillation, which was presented by 63 patients. The other indications are shown in table 2. Fifty-five percent of the patients (n=70) presented therapeutic INR levels on the day of the blood collection.

From the 127 patients in the study, 6.3% (n=8) had to repeat the finger prick collection due to preanalytic errors (small drop of blood and incorrect application of blood on the test strip).

An asymmetrical distribution of the INR values measured with the point-of-care device and the control method was found. The correlation between the INR measurements of the Coaguchek S™ system and our laboratory's standard method is shown in figure 1. The Spearman (r_s) coefficient was 0.90 (p<0.0001; CI:95% 0.87-0.93) between the Coaguchek S™

Table 1 - Characteristics of the study population

Characteristic	Patients (n=127)
Male Gender	55%
Age	58 ± 14
White Race	90%
Anticoagulant	
Phenprocoumon	61%
Warfarin	39%
Weekly dosage	20mg ± 0.5
Phenprocoumon	14 ±7
Warfarin	29 ±12
No. of months using OAC	36* (1-240)

*OAC - oral anticoagulant; *median.*

Table 2 -Oral anticoagulant indications

Indication	Patients (n=127)
AF	49.6% (63)
Metal Prosthesis	37% (47)
PE	2.4% (3)
DVT	0.8% (1)
AMI	3.1% (4)
HF	2.4% (3)
Others	4.7% (6)

AF - atrial fibrillation; PE - pulmonary embolism; DVT - deep vein thrombosis; AMI - acute myocardial infarction; HF - heart failure.

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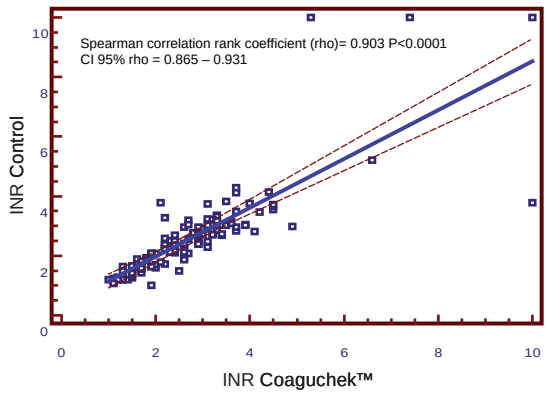

Fig. 1 - *Average INR correlation graph for the Coaguchek S™ system and control method.*

systemand the control method.

The average INR with the Coaguchek S™ system was 2.75 ± 1.40 INR units. The average INR with the conventional method was 2.59 ± 1.41 INR units. The Coaguchek S™ system overestimated the INR values by 0.15 units for all measurement levels (CI 95% = 0.007 – 0.309). Figure 2 shows a graphic representation of this difference (bias), when compared with the average of the two measurements – Coaguchek S™ system and laboratory method. In this figure the margin of error of the measurements from the Coaguchek S™ system, capillary prothrombin time, and confidence interval are shown.

Table 3 shows the average difference (bias) and the standard deviation between the different INR ranges; less than 2, between 2 and 3, between 3.01 and 3.5, and greater than 3.51 INR units.

The INR values varied from 1.01 to 10, based on the control method used in our Institution. Based on these data, 55.1% (70/127) of the patients had therapeutic INR levels; 33.1% (42/127) were below the therapeutic level and 11.8% (15/127) had anticoagulation levels above 3.5 INR units. With the Coaguchek S™ system, 52.1% (67/127) of the patients had therapeutic INR levels; 29.9% (38/127) were below the therapeutic level and 17.8% (22/127) had anticoagulation levels above 3.5 INR units. The Kappa agreement index was 73.5% (Table 4).

In relation to medical decisions based on the new system in comparison to the control method, the Coaguchek S™ system indicated an unnecessary dosage adjustment in 23 cases (18%). Seven of the patients would require higher anticoagulation dosages, but if the interval of 2 to 3.5 INR units obtained on the Coaguchek™ was considered this would not occur. Three cases, that were already at therapeutic levels, would have their dosages increased, 10 cases would have their dosages reduced unnecessarily, and the dosages for 3 patients with INR values above 3.5 would remain unchanged. (Table 4).

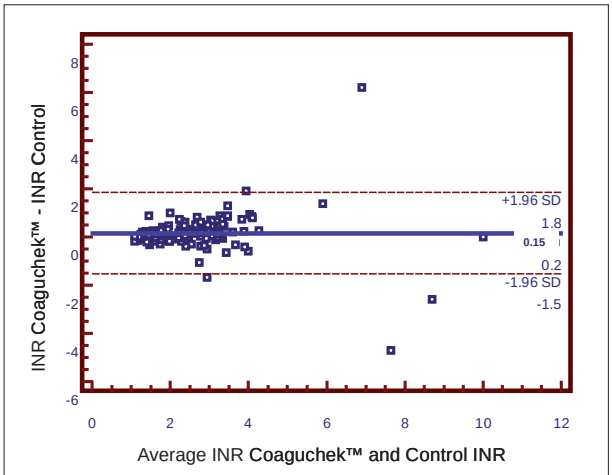

Fig. 2 - *Bland-Altman Graph of Differences between the INR results for the Coaguchek S™ system and the control method represented on the graph as the mean difference of the INR values. Standard Deviation = 0.857.*

Table 3 - Average difference and margin of error between the INR measured using the Coaguchek S™ system and laboratory methods

INR Category	n	Difference	Standard Deviation
< 2	42	0.12	0.29
2.01 – 3.0	50	0.25	0.42
3.01 – 3.5	20	0.15	0.56
>3.51	15	0.01	2.32
Average of all categories	127	0.15	0.85

Table 4 - Percentage of agreement and Kappa index in the comparison between the Coaguchek S™ system and the control method

INR Coaguchek	INR < 2	INR = 2 – 3.5	INR > 3.5	Total (%)
Control				
INR <2	35	7	0	42 (33.1)
INR 2 – 3.5	3	57	10	70 (55.1)
INR > 3.5	0	3	12	15 (11.8)
Total (%)	38 (29.9)	67 (52.8)	22 (17.3)	127

Kappa = 0.735 Standard Deviation (Kw'=0) = 0.066 Standard Deviation (Kw'#0) = 0.050.

Discussion

The relation between dosage and therapeutic response varies greatly for oral anticoagulant medication. For this reason, frequent prothrombin time monitoring is required for patients using this type of medication.

INR is the recommended prothrombin time control method. Results in INR units facilitates the comparison of measurements from different systems and laboratories[10].

The advent of portable prothrombin time control systems offers substantial advantages for managing this patient population[5,11]. It is of utmost importance to choose a system with proven reliability so that the measurement is as accurate as possible.

For this study, we considered our central laboratory's method to be the most accurate system for prothrombin time control, as it uses highly sensitive human thromboplastin (ISI=1), as recommended by the College of American Pathologists[12].

Various studies have proven the good correlation between the Coaguchek S™ system and laboratory measurements[3,13,14]. Medical centers like the Mayo Clinic have used the technology of these devices to manage their patients[6]. This prothrombin time control method had not yet been tested in Brazil.

The correlation between the INR values obtained with the Coaguchek S™ system and the laboratory tests was almost perfect[15] with a r_s coefficient equal to 0.9, similar to the findings of other studies involving the Coaguchek S™ system and other prothrombin time control devices[6,16,17]. However, according to Bland and Altman[7], correlation coefficients are not the best method to evaluate measurements between two methods, since this merely reveals the variation between the two results and not the absolute difference. Therefore, two tests could present a perfect correlation despite a systematic and significant difference between the methods. The best method to describe the result would be the difference of the averages including the margin of error.

In our study, the Coaguchek S™ system overestimated the INR measurements by 0.15 units with a standard deviation of 0.85 INR units. In addition, as the INR value becomes higher the standard deviation also increases. The INR measurements are very reliable between 1 and 2 INR, reliable between 3.01 and 3.5 and relatively reliable between 2.01and 3.

Previous studies also report this consideration[6,17]. The quality of the Coaguchek S™ system is impaired for INR units above 4 when compared to laboratory measurements using sensitive thromboplastin. A study conducted at the Cleveland Clinic[18], using a laboratory control method similar to the one used at our hospital (Sysmex coagulation analyzer and Dade Behring human thromboplastin with ISI=1), also revealed alterations in INR values greater than 4 units. That study evaluated two other devices, the AvoSure PT Pro System (AvoSure device; Avocet Medical Inc., San Jose, CA) and the ProTime Microcoagulation System (ProTime device; International Technidyne Corporation Limited, Edison, NJ). The bias for the ProTime and AvoSure systems were 0.5 ± 0.4 and 0.4 ± 0.5 INR units, respectively, which are higher than the values found for the Coaguchek S™ system in our study (0.2 ±0.8).

In relation to agreement of the results for the intervals 1-2, 2-3.5 and > 3.5 the Kappa index was 73.5%, which according to literature is a substantial level of agreement[19]. However, based only on the portable system, the medical decisions for 18% of the cases in our study would have changed. If all Coaguchek S™ device measurements above 3.5 INR were repeated in the central laboratory this value would drop to 10%. This value agrees with the study published by Chapman and associates[20] where an 8% margin of error was found for medical decisions based on the Coaguchek™ system.

No clinical studies have been conducted to compare the safety of this device in relation to the occurrence of relevant outcomes (incidence of bleeding and embolisms). Nevertheless, the use of this type of device in anticoagulation clinics and for self management by the patient is common in England[21].

The Coaguchek S™ system has an acceptable level of agreement with the laboratory values for the two main oral anti-coagulant therapy indications: prosthetic heart valves and atrial fibrillation. According to Cannegieter[22], who analyzed over 1,600 patients in an anticoagulation clinic in the Netherlands (prosthetic valve recipients) the incidence of hemorrhagic phenomena and embolic events was lower in the interval between 2.5 and 4.9 INR units. The use of the Coaguchek S™ device to control prothrombin time in the patients with atrial fibrillation appears to be safe. This is due to the fact that the target INR value for patients with this arrhythmia should be maintained between 2 and 3. The odds ratio for patients who present INR levels below 2 is 1.9 for the occurrence of embolic events. The incidence of hemorrhagic events is 3 events in 100 patients per year for those with an INR over 4 units[23].

Potential limitations of our study were the inclusion of patients with INR values as high as 10 (most studies exclude patients with INR >7) since it is known that elevated INR results tend to increase the discrepancy between the measurements; and two measurements for each method to analyze reproducibility were not conducted.

Based on the data of our study, we found that the Coaguchek S™ system can be used to monitor prothrombin time in patients using oral anticoagulant medication in an outpatient anticoagulation clinic as long as any values above 3.5 INR units are confirmed by measurements conducted in the central laboratory.

We believe that a randomized clinical trial to compare prothrombin time control between two groups of patients, one using the Coaguchek S™ system and the other conventional laboratory measurements in relation to relevant clinical outcomes (ex. bleeding, stroke) and therapeutic interval times is the best method to evaluate the safety and effectiveness of this device for widespread use.

Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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