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Full Length Article

Accuracy of point of care coagulometers compared to reference laboratory measurements in patients on oral anticoagulation therapy☆

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ABSTRACT

Background: Vitamin K antagonists (VKA) are widely prescribed throughout the world. Patients on VKA therapy require international normalized ratio (INR) monitoring of venous blood to ensure the response remains within the therapeutic window. Point-of-care devices (POC-INR) can safely and easily monitor VKA efficacy but need to be evaluated in practice. The aim of this study was to assess the precision and accuracy of a new POC-INR (Qlab) compared to the laboratory plasma technique and the CoaguChek-XS system.
Methods: Consecutive patients on VKA referred to our institution were included. The study was designed to analyze 75 patients divided equally in the following subgroups: INR < 2; INR = 2–3; INR > 3. INR was measured with an established laboratory method (INRREF) with an international sensitivity index of 1.0 and by two different POC-INRs: the Qlab (INRQlab) and the CoaguChek-XS systems (INRXS).
Results: 82 patients treated mainly for atrial fibrillation or venous thromboembolism disease were included. Precision in therapeutic range (INR = 2–3) of both POC-INRs was satisfactory with a coefficient of variation of 4.6% for the Qlab and 4.3% for the CoaguChek-XS. INRRef was 2.70 ± 1.36, INRQlab 2.59 ± 1.25 and INRXS 2.89 ± 1.37. Accuracy was low with the Qlab ($R^2 = 0.64$) and higher with the CoaguChek-XS ($R^2 = 0.94$). The mean relative difference from the INRRef was higher for the Qlab (18.4%) than for the CoaguChek-XS (12.9%). Clinical concordance was lower with the Qlab (78.2%) than with the CoaguChek-XS (90.0%).
Conclusion: This study suggests that the Qlab has accuracy limitations with clinical consequences. New POC-INR devices require careful evaluation prior to clinical implementation.

1. Introduction

Current international guidelines recommend anticoagulation as thromboprophylaxis in several cardiovascular diseases such as atrial fibrillation, pulmonary embolism and mechanical valve replacement [1–3]. Despite the emergence of new direct oral anticoagulants, vitamin K antagonists (VKA) remain a first-line treatment for oral anticoagulant therapy worldwide [4]. However, VKA treatment must be regularly monitored within a tight therapeutic window to avoid both thrombotic and bleeding complications and ensure safety and efficacy. The gold standard method for monitoring VKA therapy is prothrombin time (PT) testing of plasma collected via venipuncture. The PT is expressed as an international normalized ratio (INR) to limit variability of measure due to the thromboplastin reagent. However, INR monitoring requires frequent venous blood sampling for patients and frequent trips to laboratories, which reduces compliance. The point-of-care INR coagulometers (POC-INR) requiring a minimal blood sample volume are a simple tool to facilitate patient monitoring. POC-INRs can be used at the patient's convenience and produce a fast INR result allowing prompt VKA dose adjustment. These meters are widely used in Europe for self-monitoring and self-management. Unfortunately, POC-INRs are underused in France and reserved mainly for children. All POC-INR systems need to be evaluated before routine use by patients [5–7]. The primary objective of this study was to evaluate a new POC-INR device (Qlab) for precision and accuracy compared to laboratory INR measurement and another validated POC-INR system (CoaguChek-XS) [5–12].

Abbreviations: INR, international normalized ratio; ISI, international sensitivity index; POC, point-of-care; PT, prothrombin time; VKA, vitamin K antagonist.

☆ None of the authors have any relationship to disclose relevant to the contents of this paper.

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2. Methods

2.1. Study population

This prospective study was conducted in the Department of Cardiology and the Anticoagulation Clinic (CREATIF) at Lariboisiere Hospital, Paris, France, between February 2014 and April 2014. We included consecutive patients (male or female), aged ≥18 years, under VKA treatment (warfarin or fluindione) for whom the INR was assessed. Patients were excluded if they had previously been treated for myeloproliferative neoplasms, had a platelet count outside the 100–500G/L range, were receiving another anticoagulant (e.g. unfractionated heparin) or if the VKA treatment had been initiated <7 days previously. To analyze the accuracy over a large range of INRs, three groups of 25 patients were analyzed: INR < 2; INR = 2–3; INR > 3. Once 25 patients had been included for one subgroup, inclusion in that subgroup was stopped and inclusion in the other subgroups maintained until the required number was reached ($n = 75$).

The following data were systematically recorded: age, sex, cardiovascular risk factors (diabetes mellitus defined as treated or HbA1c >6.5%, treated hypertension, dyslipidemia defined as statin treatment or an LDLc level > 1.60 g/L, active smoking), body mass index, duration of VKA treatment and the following usual laboratory parameters: hemoglobin and complete blood count, fibrinogen level, PT and activated partial thromboplastin time. The study protocol complied with the Helsinki II declaration and was approved by the local scientific committee (IRB 00006477). All patients gave their informed consent for laboratory testing.

2.2. Sample and data collection

Two capillary blood samples followed by a venous sample were obtained from each patient. Two separate finger-stick tests were performed to obtain the blood droplet samples for the INR calculation by the CoaguChek-XS and Qlab systems (INRXS and INRQlab respectively). For each patient, the first drop was alternated between both systems to even out possible sampling differences.

2.2.1. New coagulometer device

The Qlab platform (Micropoint Bioscience, Santa Clara, California, USA) consists of a small electrometer and disposable test strips. The meter measures the change in impedance of the blood-reagent-mixture during the process of coagulation and determines the PT using a specific algorithm. The thromboplastin of this new device is a human recombinant with an international sensitivity index (ISI) of about 1. A drop of about 10 μl of capillary blood is applied to the sample application area of the test strip and the INR measurement is displayed after 2 min. For our study, an investigator recorded the resulting INRs on a data sheet. Quality control was performed using liquid controls on separate strips. Two different Qlab meters were used alternately during the study.

2.2.2. CoaguChek-XS system

The CoaguChek-XS (Roche Diagnostics, Basel, Switzerland) also uses a human recombinant thromboplastin with an ISI ≈ 1. For each test with the CoaguChek-XS system the Softclix device (Roche Diagnostics, Basel, Switzerland) was used to release a drop (10–15 μl) of capillary whole blood, which was applied to the test strip. The investigator recorded the INR measurement, displayed after 1–2 min. Quality control was performed using liquid controls on separate strips.

2.2.3. Plasma INR measurement

Peripheral venous blood sampling was performed from an arm vein with a vacuum tube sampling system (Becton Dickinson system and Greiner). The tubes contained sodium citrate 0.5 ml/4.5 ml (final citrate concentration 0.105 M). Plasma was immediately prepared by centrifugation for 15 min at 2500 g (centrifugal force) and stored at room temperature for <2 h. The INR was determined instantly upon plasma preparation on a STA-R Evolution coagulometer (Stago, Asnières sur Seine, France) from an aliquot of plasma from the primary tube with thromboplastin (animal origin) with an ISI value of 1.7 (STA Neoplastin-CI, Stago, Asnières sur Seine, France). The calibration was performed according to international guidelines established by the World Health Organization [13, 14]. INR was analyzed immediately in duplicate (non-frozen samples). Hemoglobin, hematocrit, platelets, fibrinogen, and leucocytes were analyzed at the same time on fresh blood. For the two additional INR determinations, plasma was prepared by centrifugation as described above. Plasma was aliquoted by pipetting and the aliquots were immediately frozen at −80 °C, and stored for four weeks. After thawing at 37°, INR was determined instantly as described above twice in a row (frozen samples) with a thromboplastin (animal origin) with an ISI of 1.3 (STA Neoplastin-CI+, Stago, Asnières sur Seine, France) and a human recombinant thromboplastin with an ISI of 1.0 (STA Neoplastin-R, Stago, Asnières sur Seine, France). The INR measured from the stored aliquots with the STA Neoplastin-R with the lowest ISI (ISI = 1.0) was considered as the gold standard laboratory method (INRRef).

2.3. Precision and accuracy

2.3.1. Determination of reproducibility

The CV announced by the manufacturers for both systems is ≤5% and was evaluated in 10 samples in the present study. The reproducibility of the Qlab was determined using capillary blood from healthy blood donors ($n = 5$) and patients undergoing oral anticoagulation therapy with an INR between 2 and 3 ($n = 5$) using test strips with the same batch number. After capillary punctures of alternate fingers, dual measurements were performed to calculate the coefficient of variation (CV) and standard deviations (SD). In the same way, the reproducibility of the CoaguChek-XS was determined using capillary blood from patients undergoing oral anticoagulation therapy with an INR between 2 and 3 ($n = 5$) using test strips with the same batch number with dual measurements. Acceptable analytic precision was defined as a CV <5%.

2.3.2. Determination of accuracy

2.3.2.1. Linear regression. The INR results from both POC-INR systems were plotted against the laboratory measurement and the linear regression procedure which gives an assessment of agreement of methods: slope and coefficient of correlation (R^2) were performed. Regression of the line of best fit returned a slope of approaching unity, intersection with the origin.

2.3.2.2. Bland-Altman plot. Data were also displayed using plots of mean versus difference (Bland-Altman plot). The difference between the measurements was calculated together with the SD of the differences. Bland-Altman 95% limits of agreement were calculated as the mean difference between the INR pairs ± 1.96 times the SD of the difference [15].

2.3.2.3. Mean absolute and relative difference. We calculated the mean of the absolute difference [*INRRef – INRPOC*] and the relative difference ([*INRRef – INRPOC*]/*INRRef*). Acceptable analytical accuracy measured by mean absolute difference was defined as a deviation, compared to the reference measurement of ± 0.2 INR. The mean relative difference gave an accuracy rating according to Hill [16] as very good (6.58–9.25), good (9.32–11.86), acceptable (11.93–14.54), marginal (14.60–20.28) or very poor (20.34–26.99).