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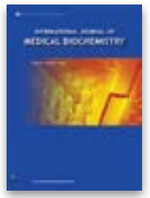

Technical Report

International normalized ratio monitoring: Agreement between point-of-care LabPad® and clinical laboratory results

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Abstract

Objectives: The Di@pason scheme, introducing a point-of-care (POC) International Normalized Ratio (INR) measurement with the LabPad® was initiated in 2019 by the French National Health Agency. The aim of our study was to assess the analytical agreement between LabPad ® and laboratory INR results, especially at sub- and supratherapeutic levels. The allowable differences were based on the accuracy requirement defined by the International Standard ISO 17593:2022 and analytical discordances versus INR Ranges.

Methods: From February 2020 to August 2022, the agreement between POC and laboratory INR results was analyzed in 83 patients. All subjects were monitored on oral anticoagulant therapy (57 patients treated with fluindione (Previscan®), 24 patients were treated with warfarin (Coumadin®) anticoagulant medication and acenocoumarol (Sintrom®) was used for two subjects).

Results: The laboratory INR results ranged from 1.2 to 10 with a mean of 3.736±1.479, and LabPad® INR ranged from 0.8 to 7.3 with a mean of 3.818±1.599. Analysis of the graph demonstrated that the INR relationship between LabPad ® and STA-R Max3 ® did not remain linear above 7.3. An extended measurement area and Pearson correlation coefficient (r) showed a significant and strong (r=0.91 [p<0.001; 95% CI: 0.81–1.00]). The regression slope was 0.980 (p<0.001; 95% CI: 0.878–1.081) and the y intercept was 0.158 (p<0.001; 95% CI: –0.251–0.566). The concordance analysis showed that 93% of the results were within the accuracy requirement defined by the international standard ISO17593:2022, but significant discrepancies appeared on the LabPad® for INR results above 4. According to analytical discrepancies and INR, ranges showed substantial agreement on these criteria with 88% and a Kappa coefficient of 0.67.

Conclusion: The LabPad® and laboratory INR results were highly correlated within the therapeutic range, above this range, a venous checking is recommended to confirm the results.

Keywords: Capillary sampling, international normalized ratio, monitoring, point-of-care, venous sampling

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The measurement of International Normalized Ratio (INR). is used to support the monitoring of patient oral anticoagulant therapy (OAT) with Vitamin K antagonists. These agents include warfarin (Coumadin ®), fluindione (under the brand name Previscan ®), and acenocoumarol (Sintrom ®, also sold as other brand names). The agents have a narrow therapeutics window, and their effectiveness can be impacted by the patient's diet if they eat Vitamin K-rich foods such as green and leafy vegetables, so regular monitoring is necessary. An INR calculation relies on a thromboplastin manufacturer's international sensitivity index (ISI) number, which mathematically compares a thromboplastin reagent lot to an international reference standard [1]. In 2019, the French national health agency has decided to provide the Di@pason scheme to 10,000 patients undergoing anticoagulant treatment with antivitamin K. In this project, analyse was performed by capillary measurement with the LabPad® INR device (Avulun ®, Grenoble, France) in point-of-care (POC). The aim of our study was to verify the accordance between the LabPad® INR and clinical laboratory INR measurement.

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Materials and Methods

Ethical approval

The laboratory investigations were carried out in accordance with the General Data Protection Regulation (EU Regulation 2016/679 and Directive 95/46/EC) and the French data protection law (Law 78-17 of January 6, 1978 and Decree 2019-536 of May 29, 2019), which does not require a review by an ethics committee for the secondary use of samples collected for health-care purposes. In such case, the use of elements and products of the human body for a medical or scientific purpose other than that for which they were removed or collected are possible (article L.1211-2 of the French Public Health Code). The "Labosud Database" is registered at the French National Commission on Informatics and Liberty, CNIL, under record No. 2073511v0.

Inclusion of participants

From February 2020 to August 2022, 83 patients were simultaneously drawn with a few µL of capillary whole-blood for LabPad®INR capillary testing and a venous blood tube for laboratory testing according to laboratory standard procedures. All subjects were monitored on OAT of which the majority undergoing active fluindione treatment (57 patients treated with Previscan®), 24 patients were treated with warfarin (Coumadin®) anticoagulant medication and acenocoumarol (Sintrom ®) was used for two subjects.

Analysis

The coagulometer, LabPad® INR, measures blood coagulation time thanks to a patented an optical analysis of the red cell movements that freeze when the clot is formed inside the microcuvette. The elapse time between blood drop and clot makes it possible to calculate the INR thanks to an algorithm.

Venous blood was collected in BD Vacutainer plastic citrate tubes (0.109 M, 3.2% buffered sodium citrate). The blood to additive ratio was 9:1. Each specimen was centrifuged at 2000 G for 10 min for preparation of citrated plasma and testing according to the pre-analytical deadlines recommended by the GFHT [2]. The samples were analyzed on STA R Max3 (Diagnostica Stago, Gennevilliers, France) automated coagulation analyze and included prothrombin time (PT) using STA NeoPTimal ® reagent with and an ISI very close to 1. The INR ratio is calculated as a ratio of the patient's PT to a control PT standardized for the potency of the thromboplastin reagent developed by the World Health Organization using the following formula [1]:

$$INR = (PTpatient/PTcontrol)^{ISI}$$

Comparison of techniques

Analytical agreement between LabPad® INR and laboratory results was studied by a scatter plot with regression analysis. Individual results of the oral-anticoagulation monitoring system were plotted as the dependent variable and the laboratory values as the independent variable. Identical scales and intervals were used for the X-and Y-axes. Passing-Bablok regression analysis and Spearman correlation analysis were used to evaluate the compatibility of the two methods ($p<0.05$ was considered statistically significant). The allowable differences were based on the accuracy requirement defined by the International Standard ISO 17593:2022 [2]. According to this international standard, overall agreement of 95% of the differences between results from laboratory and PoC, in the combined INR ranges, should be within the limits in:

- INR laboratory <2: discrepancy if self-measurement INR differs from laboratory INR by more than 0.4 units
- 2< Laboratory INR ≤4.5: discrepancy if self-measurement INR differs by more than 20% from laboratory INR
- 4.5< INR laboratory ≤6: discrepancy if self-measured INR differs by more than 25% from the INR. Laboratory
- INR >6: discrepancy if self-measurement INR differs by more than 30% from laboratory INR.

Analytical discordances versus INR ranges

According to the French Committee on Haemostasis and Thombosis [3], analytically discordant INR measurements remain "within an acceptable risk range" if both the laboratory and PoC were within the range [INR 1.8-5]. These discordances were considered "t of range with acceptable risk" if an INR (laboratory and/or PoC) was in increased thrombotic risk (≤1.8) or in area of increased bleeding risk (≥5). Based on these criteria, percent agreement and kappa coefficients [4] with a 95% confidence interval (CI) were calculated to estimate the agreement between all paired samples. According to Landis and Koch [5], kappa coefficients can be interpreted as one of the following six degrees of agreement: poor (<0), slight (0.01–0.20), fair (0.21–0.40), moderate (0.41–0.60), substantial (0.61–0.80), and almost perfect (0.81–1.00). The percent agreement between the paired samples was calculated as the proportion of concordant sample sets divided by the total number of samples.

Results

The laboratory INR results ranged from 1.2 to 10 with a mean of 3.736±1.479, and LabPad® INR ranged from 0.8 to 7.3 with a mean of 3.818±1.599. For the LabPad, above 7.3 INR, the plot analysis (Fig. 1a) showed that the relationship did not remain linear.

Over an extended measurement area, Pearson correlation coefficient (r) showed a significant and strong (r=0.91 [p<0.001; 95% CI: 0.81–1.00]). The regression slope was 0.980 (p<0.001; 95% CI: 0.878–1.081) and the y intercept was 0.158 (p<0.001; 95% CI: –0.251–0.566) (Fig. 1a).

Within a measurement range of 0.8–4.0 INR, Pearson correlation coefficient (r) showed an excellent correlation (r=0.94 [p<0.001; 95% CI: 0.84–1.08]). The regression slope was 0.957 (p<0.001; 95% CI: 0.834–1.081); the y intercept was –0.176 (p<0.001; 95% CI: –0.510–0.157) (Fig. 1b).

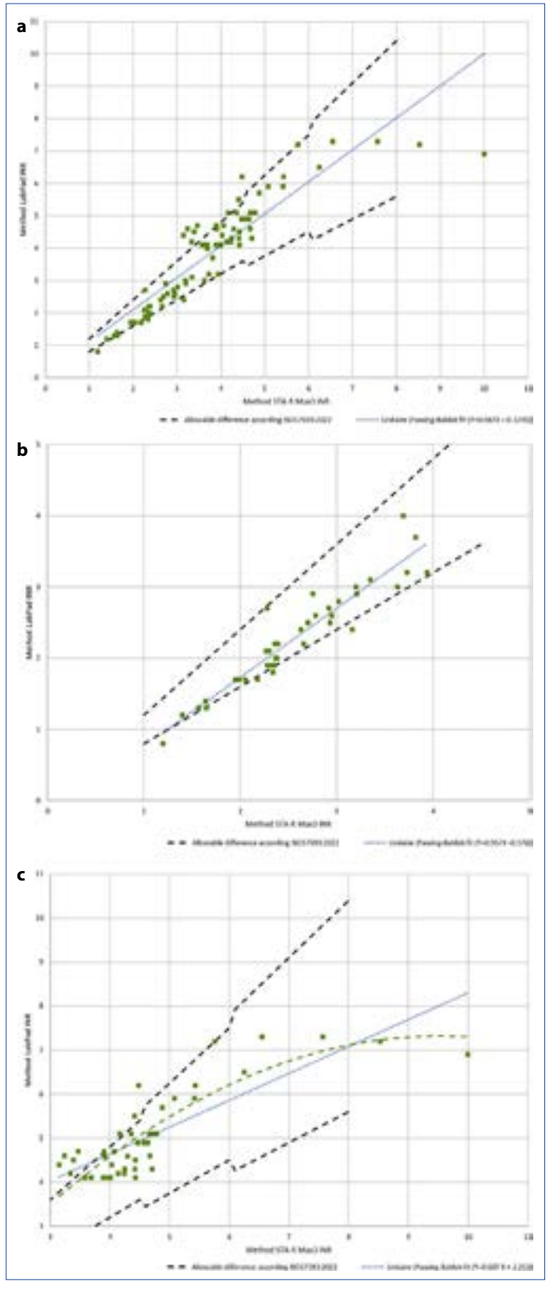

Figure 1. Scatter plot with regression analysis between LabPad® INR and laboratory results. (a) Over an extended measurement area. (b) Within a measurement range of 0.8 to 4.0 INR. (c) For a LabPad INR measurement area greater than 4.

INR: International normalized ratio.

For a LabPad INR measurement area >4, Pearson correlation coefficient (r) decreased to 0.82 (p<0.001; 95% CI: 0.64–0.99). The regression slope was 0.607 (p<0.001; 95% CI: 0.476–0.739); the y intercept was 2.21 (p<0.001; 95% CI: 1.578–2.858) (Fig. 1c).

The concordance analysis showed that 93% of the results were within the limits accuracy requirement defined by the International Standard ISO17593:2022 but significant discrepancies were appeared on the LabPad ® for INR results above 4 (Fig. 1a-c).

Percent agreement and kappa coefficients according to analytical discrepancies and INR ranges are shown in Table 1. The study showed substantial agreement on these criteria with 88% and a Kappa coefficient of 0.67. While no discrepancies were found for established thrombotic and hemorrhagic risks, false hemorrhagic risks (6/69) and false thrombotic risks (4/69) were observed. Considering the results observed, any therapeutic adjustment should be checked previously by the laboratory.

Discussion

Optimal INR scores depend on the underlying indication for treatment and patient level characteristics, but for most patients, the INR range of 2.0–4.0 was predefined as the "safety zone" [6]. Potential advantages of POC devices permit INR results to be determined immediately without a visit to a laboratory and without the need for venepuncture. This enables the immediate adjustment of OAT following testing. The LabPad® INR was much less invasive than the current venous sampling and facilitate the immediate adjustment of anticoagulant treatment by health professionals. It can be used not only in the office, but also during home visits.

The major limitations of POC devices were that they tend to underestimate high INR values and overestimate low INR values, had low thromboplastin sensitivity, were unable to calculate a mean normal PT, and certain instruments result in errors in patients with antiphospholipid antibodies [7, 8]. According to the manufacturer's package insert, the following factors can interfere and alter POC INR measurements such coadministration with XA inhibitors or low-molecular-weight heparin [9]. Use of an alternative method of measurement is recommended in the event of a transition period with a heparinized treatment.

The study by Lindström and Henriksson [10] examined capillary and venous sampling and found that capillary sampling method showed statistically significant lower values (p<0.001) for plasma PT/INR than the standard venous sampling method with a mean difference (bias) of –0.14. In 2016, the FDA requested the withdrawal from market of one manufacturer's PT/INR monitoring systems for reportedly generating inaccurate low readings [11].

Our study showed that up to INR 4.0, the correlation between the LabPad® and the laboratory analyzer was strong (r=0.94). Above 4.0, the correlation was less strong (r=0.82) and clinical discordances have emerged. The LabPad could report the INR result in a range of 0.8–8 units, but the regression analysis in Figure 1c showed that the relationship between LabPad and STA-R Max3 tended to describe a non-linear regression formalized by the green curve with a maximum LabPad value of

Table 1. Analysis of analytical discrepancies versus INR ranges according to the thrombotic and the bleeding risk

Laboratory results	Method LabPad INR			Agreement rate (%)	Kappa (95% CI)
	Below area	Within area	Above area		
Area with increased thrombotic risk INR <1.8 n=5	0	5	0	88%	0.67 (0.47–0.86)
Area with an acceptable risk (INR 1.8–5) n=69	4	59	6		
Area of increased bleeding risk, INR>5.0 n=9	0	9	0		

INR: International normalized ratio; CI: Confidence interval.

7.3 units. For INR. Higher than 4.0, we recommended nurses to collect a venous sample for laboratory control before adjustment of anticoagulant treatment.

Validation and performance monitoring of POC devices INR results by a clinical laboratory were essential. It should also be noted that the implementation of a quality management system for POC INR devices is necessary to ensure the reliability of INR results. This may be an internal quality control (provided by the manufacturer) performed by the laboratory when the health-care professional visits the clinical laboratory. It is also possible comparing periodically capillary and venous sampling results the results for a patient. The precision of the LabPad INR test, calculated using 100 different devices, showed that the CV% was 5.9% with a mean value of 1.7 INR and 3.3% with a mean value of 3.3 INR. Moreover, an external quality assessment scheme provided by Labquality Oy® was proposed to compare the performance of POC INR devices with other users. The May 2022 survey showed an average bias of +7.0% for the LabPad INR group compared to all POCT manufacturers.

Under Di@pason scheme, the clinical biologists who supply the nurses with the *in vitro* diagnostic devices were at the heart of the experimentation, training them, empowering them, and supplying them with consumables. They carried out regular quality controls of the devices (qualification and maintenance of test performance). The device had an interface to connect to laboratory information systems and transmit data to the clinical biologist, which validate the results remotely and initiate emergency treatment if necessary. This approach was a strength compared patient self-testing strategies, which showed potential disadvantage that less professional guidance may result in poorer regulation of oral anticoagulant treatment [12].

Conclusion

LabPad®INR offers an alternative to laboratory-based testing and venepuncture, enabling INR determination from a fingerstick sample of whole blood. They permit INR results to be determined immediately, allowing for more rapid medication adjustments. The LabPad® and laboratory INR results were highly correlated within the therapeutic range, above this range, a venous checking is recommended to confirm the results. The inclusion of subjects monitored on OAT in this study resulted in restricted recruitment of high and low INR samples.

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