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International normalized ratio (INR) testing in Europe: between-laboratory comparability of test results obtained by Quick and Owren reagents

A collaborative study from the European Committee for External Quality Assurance Programmes in Laboratory Medicine (EQALM)

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Abstract

Background: This study was designed to obtain an overview of the analytical quality of the prothrombin time, reported as international normalized ratio (INR) and to assess the variation of INR results between European laboratories, the difference between Quick-type and Owren-type methods and the effect of using local INR calibration or not. In addition, we assessed the variation in INR results obtained for a single donation in comparison with a pool of several plasmas.

Methods: A set of four different lyophilized plasma samples were distributed via national EQA organizations to participating laboratories for INR measurement.

Results: Between-laboratory variation was lower in the Owren group than in the Quick group (on average: 6.7% vs. 8.1%, respectively). Differences in the mean INR value between the Owren and Quick group were relatively small (<0.20 INR). Between-laboratory variation was lower after local INR calibration (CV: 6.7% vs. 8.6%). For laboratories performing local calibration, the between-laboratory variation was quite similar for the Owren and Quick group (on average: 6.5% and 6.7%, respectively). Clinically significant differences in INR results (difference in INR > 0.5) were observed between different reagents. No systematic significant differences in the between-laboratory variation for a single-plasma sample and a pooled plasma sample were observed.

Conclusions: The comparability for laboratories using local calibration of their thromboplastin reagent is better than for laboratories not performing local calibration. Implementing local calibration is strongly recommended for the measurement of INR.

Keywords: between-laboratory variation; international normalized ratio (INR); local calibration; Owren; Quick.

Introduction

Following the introduction of the vitamin K antagonist warfarin as a medication in 1954 [1], the use of the synthetic derivative of dicoumarol has grown to the extent where it is one of the most widely prescribed oral anticoagulant drugs in the Western hemisphere. The use of vitamin K antagonists in oral anticoagulation is known to substantially reduce the incidence of thromboembolic events [2]. A recent report from a large-scale retrospective study initiated in 2008 of over 29,000 patients indicates that approximately four million patients are treated with warfarin per year in the USA [3]. Treatment with vitamin K antagonists is monitored by the measurement of the prothrombin time (PT).

The PT was developed by Quick [4] as a screening test for the extrinsic (tissue) clotting system and has over time become a globally utilized method, particularly following acceptable PT standardization using the PT ratio and subsequent calculation of the international normalized ratio (INR) [5]. Further tests were developed and designed for anticoagulant control, known as the Owren method [6] with subsequent development of a reagent named thrombotest [7]. In the Owren method, tissue factor is combined

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with adsorbed plasma as a source of fibrinogen and factor V. Furthermore, the dilution factor of the test plasma in Owren's method is greater than in Quick's method. Owren tests are used extensively in Scandinavian countries. It has been shown that there can be clinically important significant differences in the measurement of INR between the Quick and Owren method [8–11].

Differences between thromboplastin reagents used in the determination of INR by Quick methods are known to affect results and may influence patient management, especially at higher INR levels [12].

Previous publications have noted an improvement in INR results after local calibration for both Quick [13] and Owren-type reagents [14]. It has also been shown that differences can be minimized by local International Sensitivity Index (ISI) correction [15].

To our knowledge, a large international multicenter comparison of the Quick and Owren method by measuring the INR in a set of control samples has never been performed.

Therefore, the European Committee for External Quality Assurance Programmes in Laboratory Medicine (EQALM) Working Group on Haemostasis initiated a project amongst their members to compare INR results, in European countries. EQA organizations from 10 different European countries participated in this project. In total, 618 laboratories returned results, resulting in the largest comparative INR study so far undertaken in Europe. The aim of the study was (a) to compare the results from participants using Quick-type reagents with those from participants using Owren-type reagents, (b) to compare the results obtained after local calibration with those obtained by participants performing no local calibration and (c) to investigate the comparability of single-donor plasma against pooled plasma.

Materials and methods

Participating laboratories were recruited by national External Quality Assessment (EQA) programs in 10 European countries. Each laboratory received a set of four different lyophilized, buffered (HEPES) plasmas: samples 1 and 2 with a target INR between 2.0 and 2.5 and samples 3 and 4 with a target INR level in the 3.0–3.5 range. Samples 1 and 3 were single-donor plasmas, and samples 2 and 4 pooled donor plasmas.

The plasma pools 2 and 4 were prepared from at least 10 different donors. All samples were prepared by UK NEQAS for Blood Coagulation, Sheffield, United Kingdom.

Samples were distributed by the national EQA organizations. The following organizations participated in this study with the number of participants in parentheses: AFSSAPS, France (n = 105); CEQA, Croatia (n = 26); DEKS, Denmark (n = 63); Equalis, Sweden (n = 76); INSTAND, Germany (n = 27); Labquality, Finland (n = 10); NOKLUS, Norway (n = 72); RoEQALM, Romania (n = 15); SKML, the Netherlands (n = 121); WIV-ISP, Belgium (n = 103). Results had to be returned on standard report forms, including information on the reagent and equipment used and the application (or not) of local calibration. All reported information and results were managed centrally in the offices of the ECAT Foundation, Voorschoten, The Netherlands. Statistical analyses were performed with the software package SPSS version 19.0. Differences in between-laboratory variation were tested by Snedecor's F-test, whereas differences between INR values were tested by Student's t-test. The level of significance used was 0.05.

For each sample, all results were pooled together and the mean and standard deviation (SD) were calculated. Results deviating by more than three times the standard deviation (mean plus or minus 3 SD) were identified as outliers and were not included in this study. The number of outliers varied between 1.8% and 2.8%. Between-laboratory variation was expressed as the coefficient of variation (CV): $CV = 100 \times SD/(mean)$.

The Owren-type reagents used by the participants in this study were Owrens PT (Medirox), Nycotest PT (Axis-Shield), Thrombotest PT (Axis-Shield), SPA 20/50 (Stago) and Hepato Quick (Stago).

The Quick-type reagents used were PT-Fib-HS (Instrumentation Laboratory), PT-Fib-Recomb (Instrumentation Laboratory), Recombiplastin (Instrumentation Laboratory), Recombiplastin 2G (Instrumentation Laboratory), Thromboplastin DS (Pacific Hemostasis), Innovin (Siemens), Thromborel S (Siemens), Neoplastin CI (Stago), Neoplastin CI Plus (Stago), Neoplastin R (Stago), Technoplastin HS (Technoclone), Simplastin Excel S (Trinity Biotech), Simplastin HTF (Trinity Biotech) and Simplastin LS (Trinity Biotech).

Results

Overall results

The mean INR values (range of minimum and maximum reported values by the participants) for samples 1 and 2 are 2.12 (1.59–2.69) and 2.55 (1.87–3.26), respectively. For samples 3 and 4, the mean INR values are 3.09 (2.01–4.32) and 3.27 (2.40–4.20), respectively. The mean value of each of the samples is in or close to the intended INR range (see Materials and methods). Samples 1 and 2 with lower INR values show a slightly lower between-laboratory variation (CV%: 7.1 and 7.5%, respectively) than samples 3 and 4 with higher INR values (CV%: 8.7 and 8.0%, respectively). A statistically significant difference in the between-laboratory variation can only be observed between plasma 1 (single-donor plasma) and plasma 2 (pooled plasma) (F-statistic: 1.62; $p < 0.0001$). The between-laboratory variation for the samples with an INR range 2.0–2.5 is lower for the single donor plasma. For the samples with an INR range 3.0–3.5, the between-laboratory variation is lower for the pooled plasma. The results per reagent are summarized in Table 1.

Table 1: Overview of the INR results (mean [CV%]) for reagents with at least 10 participants.

Reagent	No	Sample 1	Sample 2	Sample 3	Sample 4
Owren reagents					
Owrens PT (Medirox)	59	2.05 (4.0)	2.56 (5.1)	3.06 (4.9)	3.26 (5.5)
Nycotest PT (Nycomed)	50	2.10 (5.7)	2.57 (7.8)	3.07 (8.1)	3.27 (7.3)
SPA 20/50 (Stago)	99	2.04 (5.9)	2.54 (6.7)	2.90 (6.9)	3.22 (7.8)
Hepato Quick (Stago)	26	2.08 (2.4)	2.60 (2.8)	3.03 (2.4)	3.30 (2.7)
Quick reagents					
PT-Fib-Recomb (Instrumentation Laboratory)	16	2.47 (9.3)	2.96 (9.8)	3.59 (21.2)	3.80 (11.3)
Recombiplastin (Instrumentation Laboratory/Hemoliance)	40	2.25 (6.2)	2.65 (6.4)	3.12 (7.4)	3.49 (7.4)
Innovin (Siemens)	104	2.11 (5.2)	2.39 (5.0)	3.09 (6.5)	3.11 (6.1)
Thromborel S (Siemens)	55	2.16 (6.5)	2.55 (6.7)	3.03 (6.9)	3.29 (7.3)
Neoplastin CI (Stago)	38	2.21 (4.3)	2.58 (5.4)	3.30 (4.8)	3.29 (4.9)
Neoplastin CI Plus (Stago)	74	2.15 (3.4)	2.62 (3.8)	3.25 (4.9)	3.33 (4.5)
Neoplastin R (Stago)	10	2.20 (5.0)	2.61 (6.1)	3.22 (7.8)	3.48 (4.6)

Quick and Owren method results

Approximately 40% of the participants used a PT assay based on the Owren principle, and 60% a test based on the Quick principle. A reliable comparison between these two assay principles is therefore possible in this study.

Table 2 compares the results obtained by the Quick and Owren method reagents. The mean values obtained by the participants using a Quick-type reagent are higher than those obtained by the participants using an Owren-type reagent, although the differences are relatively small and not clinically relevant (<0.20 INR). For samples 1, 3 and 4, the differences are statistically significant ($p < 0.01$). For all samples, the between-laboratory variation is statistically significantly lower in the Owren group than in the Quick group ($p < 0.05$).

Local calibration

Approximately 55% of the participants performed a local INR calibration (Owren reagent group: 217 out of 245, 89%; Quick reagent group: 119 out of 365, 33%), using an INR calibration set either of commercial origin (n = 132) or obtained from an EQA organization (n = 204). These calibration sets consist of a set of plasma samples with assigned INR values and are used to calibrate their local PT measurement system [16]. This group included six participants carrying out a full local ISI calibration of the PT reagent used. Except for eight participants, who did not indicate whether or not they had performed a local calibration, all other participants did not apply a local INR calibration.

Table 3 compares the results obtained with and without the performance of a local INR calibration, irrespective of the type of assay used.

The between-laboratory variation in the calibration group is on average 2% lower than in the non-calibration group. This difference is statistically significant for all samples ($p < 0.0001$). The mean INR values are lower in the calibration group than in the non-calibration group. Although the differences in these mean values are relatively small and not clinically relevant (<0.15 INR), for all samples they are statistically significant ($p < 0.001$).

Table 2: Comparison of the INR results obtained by the Quick- and Owren-type reagents.

Method	Sample 1		Sample 2		Sample 3		Sample 4	
	Quick	Owren	Quick	Owren	Quick	Owren	Quick	Owren
Number	362	243	363	240	354	245	357	245
Mean	2.17	2.05	2.55	2.54	3.16	2.99	3.29	3.23
Minimum	1.59	1.60	1.87	1.89	2.01	2.27	2.40	2.40
Maximum	2.69	2.53	3.26	3.02	4.32	3.98	4.20	3.94
CV, %	6.9	5.8	8.2	6.7	8.9	7.0	8.5	7.4
F-statistic	1.49		1.42		1.70		1.34	
p-Value	$p < 0.001$[a]		$p < 0.01$[a]		$p < 0.0001$[a]		$p < 0.05$[a]	

[a]Statistically significant difference.

Table 3: Comparison of the INR results obtained with and without the performance of local calibration.

Local calibration	Sample 1		Sample 2		Sample 3		Sample 4	
	No	Yes	No	Yes	No	Yes	No	Yes
Number	264	333	266	329	256	335	261	333
Mean	2.18	2.08	2.58	2.51	3.16	3.03	3.29	3.22
Minimum	1.59	1.71	1.87	1.89	2.01	2.27	2.40	2.62
Maximum	2.69	2.53	3.26	3.02	4.32	4.09	4.20	3.94
CV, %	7.8	5.8	8.5	6.8	8.9	7.6	9.0	6.8
F-statistic	1.87		1.62		1.75		1.83	
p-Value	$p < 0.0001^a$		$p < 0.0001^a$		$p < 0.0001^a$		$p < 0.0001^a$	

[a]Statistically significant difference.

Table 4: Comparison of the INR results obtained by the Owren assay group with and without the performance of local calibration.

Local calibration	Sample 1		Sample 2		Sample 3		Sample 4	
	No	Yes	No	Yes	No	Yes	No	Yes
Number	26	212	27	208	27	213	27	213
Mean	2.00	2.05	2.47	2.55	2.93	2.99	3.12	3.24
Minimum	1.60	1.71	1.90	1.89	2.40	2.27	2.40	2.62
Maximum	2.18	2.53	2.74	3.02	3.22	3.98	3.44	3.94
CV, %	8.9	5.6	9.9	6.4	7.2	7.2	11.0	6.8
F-statistic	2.38		2.28		0.96		2.40	
p-Value	$p < 0.001^a$		$p < 0.002^a$		$p = 0.959$		$p < 0.001^a$	

[a]Statistically significant difference.

Only small differences (<0.1 INR) were observed in the mean INR values between the users of commercial calibration sets and those using calibration sets provided by EQA organizations (data not shown).

The majority of the participants in the Owren group (89%) performed a local INR calibration, whereas only one third of the participants in the Quick group (33%) did so. Both assay groups were evaluated as to whether or not local calibration had affected the between-laboratory variation. This evaluation is summarized in Table 4 for the Owren assay group and in Table 5 for the Quick assay group.

For the Owren assay group, the between-laboratory variation in the local INR calibration group is on average 2.8% lower than in the non-calibration group. For the Quick assay group, this is on average 1.6%. Except for sample 3 for the Owren assay group, all differences are statistically significant (Owren: $p < 0.002$; Quick: $p < 0.005$).

For the Owren group, the mean INR values are lower in the non-calibration group, whereas for the Quick group, the mean INR values are lower in the calibration group. In both cases, the differences are relatively small, in the Owren group <0.20 INR and in the Quick group <0.15 INR.

Table 5: Comparison of the INR results obtained by the Quick assay group with and without the performance of local calibration.

Local calibration	Sample 1		Sample 2		Sample 3		Sample 4	
	No	Yes	No	Yes	No	Yes	No	Yes
Number	238	121	239	121	229	122	234	120
Mean	2.19	2.13	2.60	2.45	3.20	3.09	3.34	3.19
Minimum	1.59	1.92	1.87	2.12	2.01	2.52	2.40	2.67
Maximum	2.69	2.51	3.26	2.92	4.32	4.09	4.20	3.80
CV, %	7.2	5.8	8.1	6.7	9.2	7.5	8.6	6.9
F-statistic	1.61		1.61		1.61		1.70	
p-Value	$p < 0.005^a$		$p < 0.005^a$		$p < 0.005^a$		$p < 0.002^a$	

[a]Statistically significant difference.

In the Quick group, there are two reagents (Innovin and Thromborel S) with a sufficient number of results in both the calibration (Innovin: n = 70; Thromborel S: n = 26) and the non-calibration groups (Innovin: n = 34; Thromborel S: n = 27). This makes it possible to evaluate whether at a reagent level the effect of local calibration on the between-laboratory variation can also be observed. For Innovin, the between-laboratory variation is CV is 0.5% (range: –1.2% to +0.1%) lower in the calibration group in comparison with the non-calibration group. For Thromborel S, the difference is 1% (range: –1.5% to –0.4%) lower. Table 6 shows that in almost all cases, the between-laboratory variation in the calibration group is lower than in the non-calibration group. These differences are not significant.

Discussion

In this study, we were able to evaluate on a large international scale using different types of samples the Quick and Owren INR determination as well as the effect of local calibration on the comparability of test results.

There were no systematically significant differences in the between-laboratory variation of results from samples derived from single-donor plasma and pooled plasma when all the results were evaluated together. This finding shows that the INR system is robust and in principle both types of plasma samples can be used by external quality assessment programs.

In this study, we found differences in three out of four samples between the mean INR value measured using Quick and Owren methods. However, these differences were relatively small. Differences between different test systems or reagents have been published previously [17–20], but in addition to this observation, we were also able to demonstrate on a large scale that the between-laboratory variation of the Owren group results was less than the

Table 6: Comparison of the INR results (mean and CV) obtained by the Innovin and Thromborel S reagents with and without performance of local calibration.

Local calibration (yes/no)	No		Sample 1		Sample 2		Sample 3		Sample 4	
	No	Yes	No	Yes	No	Yes	No	Yes	No	Yes
Innovin (Siemens)	34	70	2.15 (5.1)	2.09 (4.8)	2.41 (5.0)	2.37 (5.1)	3.13 (6.7)	3.06 (6.2)	3.15 (6.7)	3.09 (5.5)
Thromborel S (Siemens)	27	26	2.16 (6.9)	2.16 (6.5)	2.55 (7.5)	2.52 (6.0)	3.02 (7.3)	3.03 (6.3)	3.28 (7.6)	3.28 (7.0)

between-laboratory variation of the Quick group results. One of the reasons could be the larger number of different reagents included in the Quick group (n = 14) in comparison with the Owren group (n = 5). This observation shows that, although the intention of the transformation of prothrombin time results to INR results was to harmonize test results, this is in real laboratory practice not fully achievable with many different reagent and equipment combinations.

Another reason for the difference between the Quick and Owren group could be the fact that the majority of laboratories using Owren reagents had already introduced local INR calibration (89% vs. 33%). We therefore investigated whether local calibration might advance further comparability of test results between laboratories using either Owren or Quick reagents. There are two ways to perform local calibration: (a) by using a set of (lyophilized) plasmas with assigned INR values (this set can be used for "direct" transformation of a measured PT to INR) or (b) by using a set of plasmas with assigned PT for an international reference thromboplastin. This set can be used for local ISI calibration of the reagent/instrument but MNPT must be determined separately for INR calculation [21]. In this study, we did not discriminate between these two calibration procedures.

Irrespective of the type of assay used, the between-laboratory variation of participants applying local INR calibration was lower than the between-laboratory variation of participants not applying local INR calibration (Table 3).

Due to the large number of participants in the Quick group, it was possible to investigate the effect of local calibration on the between-laboratory variation of the INR measurement. In addition, the effect of local calibration was also investigated in the Owren group.

The results shown in Tables 4 and 5 indicate that in the absence of local calibration, the between-laboratory variation in the Quick group is lower than in the Owren group (on average: 8.3% vs. 9.3%, respectively). However, it should be noted that the number of participants in the Owren group without local calibration is relatively low (n = 26), which may have contributed to the higher between-laboratory variation for the Owren group.

When local calibration is applied, the between-laboratory variation becomes comparable in the Quick and Owren group (on average: 6.7% vs. 6.5%, respectively). This difference is much lower than when the whole Quick group is compared to the Owren group (on average: 8.1% vs. 6.7%, respectively).

In this study, there were two Quick-type reagents (Innovin and Thromborel S) with a sufficient number of participants in the calibration and non-calibration groups. Although on the level of each individual sample the difference in between-laboratory variation between the calibration and non-calibration groups was not significant, it is clear that also on a reagent level the average between-laboratory variation of all samples in the calibration group is lower than the non-calibration group (Innovin: 5.4% vs. 5.9%; Thromborel S: 6.5% vs. 7.3%).

This finding indicates that the between-laboratory variation of INR results is similar for both the Owren and Quick groups after local INR calibration. However, there are still small differences between the Owren and Quick group in the average INR values of the four plasma samples. Although these differences are small (≤0.10 INR), they are statistically significant ($p < 0.01$), but not clinically relevant. Within the Quick group, larger differences in the average INR values were observed which may be clinically relevant (Table 1).

On the basis of our study results, we strongly recommend implementing local calibration for INR measurement to advance the comparability of INR results between different laboratories.

It is now generally accepted in laboratory medicine that reference materials and external quality assessment samples should be commutable [22]. Although the present study was not designed to assess the commutability of the four lyophilized plasma samples, it should be noted that large differences in INR might be caused by non-commutability. For example, the mean INR determined with PT-Fib Recombinant was more than 10% greater than the mean INR with Innovin (Table 4). We cannot exclude the possibility that this difference is due to a lack of commutability of the test samples. Therefore, we suggest that future studies should be designed to assess the commutability of lyophilized plasma samples.

In conclusion, this study has shown that the comparability of INR results for laboratories using local calibration of their reagent is better than for laboratories not performing local calibration. Implementing local calibration for the measurement of INR is therefore strongly recommended. After local calibration, the between-laboratory variation of INR results is similar for both the Owren and the Quick groups. In addition, this study has shown that external quality assessment programs can use either single-donor plasma or pooled plasmas for their surveys.

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