Regular Article

Accuracy of a portable international normalized ratio monitor for patients receiving a low molecular weight heparin as a bridge pending full oral anticoagulant efficacy

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Abstract

Background: Point of care (POC) devices measuring the international normalized ratio (INR) are accurate for patients with stable disease, but their efficiency has not been prospectively assessed during the “bridging period” when patients are receiving a low molecular weight heparin (LMWH) on top of a vitamin K antagonist (VKA) until the target INR is reached.

Methods: 188 dual INR measurement using the POC (INRPOC) and the laboratory (INRLab) at the same time were consecutively determined: 69 in patients receiving LMWH+VKA (bridging group) and 119 in patients receiving only a VKA (control group). INRPOC was compared to INRLab.

Results: Test strip failure rate was higher in the bridging group than in the control group (29% vs 4%; p<0.001).

In successful tests, POC accuracy was not modified by LMWH administration: the correlation coefficients between POC and lab INR values for the bridging group and the control group were 0.81 and 0.87 respectively, and the relative measure of divergence (RMD = INRLab - INRPOC / INRLab) was lower in the bridging group than in the control group (4±7% vs 10±14%; p=0.02). Finally, clinically relevant agreement between POC and laboratory was of 90% in the bridging group and 92.1% in the control group (p=0.6).

Conclusion: With the POC used (INRatio), in patients receiving LMWH when the POC gives a result, it is as accurate as in patients not receiving a LMWH.

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Oral anticoagulant therapy is conventionally monitored by laboratory analysis of the international normalized ratio (INR) in plasma obtained by venipuncture. Based on the INR value, health care providers determine the appropriate dosage of a vitamin-K antagonist (VKA).

Self-testing (and perhaps self-management) of INR whereby selected patients analyse a drop of blood using a portable coagulometer is now widely used in routine settings in many countries. Indeed, high-quality anticoagulation, regardless of monitoring method, leads to low rates of ischemic and hemorrhage events. Therefore, as the time within therapeutic INR target range is higher when patient self testing is used [1], home INR monitoring is a reasonable alternative for appropriate (selected and trained) patients.

Point of care (POC) devices are accurate for patients with stable disease who receive long term VKA treatment, but their efficiency has not been well assessed early after cardiac surgery, and particularly during the “bridging period” when patients receive a VKA and a low molecular weight heparin (LMWH) until the target INR is reached. The results of a small retrospective study [2] suggested that the INR measured with a POC device in patients receiving concurrent LMWH and VKA may be inaccurate.

We aimed to assess the reliability of a POC analyzer in patients receiving both a LMWH and a VKA.

Methods

Study population

This prospective single center study was conducted between January and June 2008.

All consecutive patients receiving a VKA and hospitalized (out or in patients) in our cardiac rehabilitation center were eligible. Patients with a known auto-immune disease were excluded (presence of anti-phospholipid antibodies could impair the reliability of the device) [4]. All patients participating in this study provided informed consent.

It must be emphasized that this study was a survey because VKA dose was adjusted by the physician as usual on the basis of INR values from the
laboratory (INR\textsubscript{lab}). Therefore, no institutional review board approval was needed.

**Material**

All patients underwent (the same day) blood testing for measurement of INR by two methods: laboratory method (reference standard) and POC method.

The INR values from the laboratory (INR\textsubscript{lab}) were determined from citrated plasma samples of venous blood. After centrifugation to produce platelet-poor plasma, the samples were analyzed in the laboratory within 4 hours after being drawn from the patient, by use of an STA-compact analyzer (Stago, France) with thromboplastin reagent with an ISI of 1.70.

INR point of care (INR\textsubscript{POC}) measurement was done by a trained nurse with the INRatio™ system (Hemosense Inc Milpitas CS, stago France).

This device consists of a small meter and disposable test strips. It measures the change in impedance of the blood reagent mixture during the process of coagulation. INR is measured by use of whole blood obtained by a finger prick; a drop of about 15 µl is applied to the sample application area on the top of the test strip. The result is shown after about 2 minutes. In addition to the patient test channel, the test strip incorporates 2 quality control channels that contain reagents designed to clot at a predetermined time. These on board controls show test failure if the test strips have been exposed to unusual conditions (e.g., temperature, humidity...) or if the reliability of the system is impaired for another reason.

If the POC failed to give a result, the test was not attempted a second time, and the INR\textsubscript{POC} result was classified as test strip failure.

**Statistical analysis**

Results are expressed as mean±SD. P values <0.05 were considered statistically significant.

**Statistical agreement**

For all dual INR measurements (portable monitor and laboratory), the INR\textsubscript{POC} was plotted as a function of the INR\textsubscript{lab}. Regression analysis was determined laboratory ranges of <2.0, 2.0-3.0, 3.1-4.0 and >4.0: An agreement in relation to magnitude of INR was defined as, based on whether the difference between the two methods, regardless of the presence or absence of LMWt. As well, the kappa coefficient was not affected by the administration of LMWH (kappa=0.30 in the control group and 0.35 in the bridging group).

**Clinically relevant agreement**

Clinically relevant agreement was defined as, based on whether the difference between the dual INR measurements would be likely to result in different VKA dosing with each INR result. Results were considered clinically concordant when both INR (POC and lab) were within the therapeutic range when both were above the therapeutic range, when both were below the therapeutic range or when one was within the therapeutic range and the other was below or above but within a 0.25 INR-units difference.

**Results**

188 dual INR measurements using the POC and the laboratory methods were consecutively determined: 69 in patients receiving LMWH + VKA (bridging group) and 119 in patients receiving only a VKA (control group).

In the bridging group, the LMWH used was always enoxaparin (100 iu/kg twice a day). The VKAs were fluindione, acenocoumarol or warfarin.

Among the 188 measurements, test strip failure rate was of 29% (n=19) in the bridging group and 4% (n=5) in the control group (p<0.001).

Therefore we analyzed 164 dual INR measurements from 88 patients (bridging group: n=50, control group: n=114). Indications for anticoagulants were: heart valve surgery (n=63), atrial fibrillation (n=19), severe dilated myocardopathy (n=4), and pulmonary embolus (n=2). Characteristics of the patients are detailed Table 1.

Differences between the patients of the bridging and the control groups were mainly due to most of the patients of the bridging group having undergone surgery less than 1 month before (86%). Therefore, these patients had, on average, lower haemoglobinemia and higher white blood cell count than did the patients of the control group. Moreover, low-dose aspirin was often prescribed in the bridging group, probably because the target INR was not yet obtained in these patients. The mean lab INR (see Table 2) was higher in the control group than in the bridging group (2.75±1.00 vs 1.89±0.45; p<0.01) which was explained by LMWH administration being stopped when the target INR was reached.

The correlation coefficient for point of care and laboratory INR values for the bridging and control groups were 0.81 and 0.87 respectively (Fig. 1). This indicates a similar degree of correlation between the two methods, regardless of the presence or absence of LMWH. As well, the kappa coefficient was not affected by the administration of LMWH (kappa=0.30 in the control group and 0.35 in the bridging group).

**Table 1**

<table>
<thead>
<tr>
<th>Characteristics of the patients.</th>
<th>Bridging group (n=50)</th>
<th>Control group (n=114)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y)</td>
<td>62 ± 11</td>
<td>62 ± 13</td>
<td>0.9</td>
</tr>
<tr>
<td>Male gender (%)</td>
<td>74%</td>
<td>59%</td>
<td>0.08</td>
</tr>
<tr>
<td>BMI</td>
<td>26 ± 4</td>
<td>26 ± 4</td>
<td>0.5</td>
</tr>
<tr>
<td>Creatininemia (µmol/l)</td>
<td>82 ± 23</td>
<td>90 ± 22</td>
<td>0.06</td>
</tr>
<tr>
<td>Haemoglobinemia</td>
<td>10.1 ± 1.4</td>
<td>11.4 ± 1.5</td>
<td>0.02</td>
</tr>
<tr>
<td>Wc count</td>
<td>7 366 ± 2 409</td>
<td>6 444 ± 1893</td>
<td>0.01</td>
</tr>
<tr>
<td>Platelet count</td>
<td>371 000 ± 131 000</td>
<td>335 000 ± 174 000</td>
<td>0.2</td>
</tr>
<tr>
<td>Crp level (mg/l)</td>
<td>19 ± 20</td>
<td>19 ± 25</td>
<td>0.9</td>
</tr>
<tr>
<td>Heart surgery</td>
<td>86%</td>
<td>40%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>&lt;1 month</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aspirin</td>
<td>62%</td>
<td>33%</td>
<td>0.005</td>
</tr>
<tr>
<td>Clopidogrel</td>
<td>4%</td>
<td>4%</td>
<td>0.9</td>
</tr>
<tr>
<td>Vka indication:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- heart valve surgery</td>
<td>42 (84%)</td>
<td>94 (82.5%)</td>
<td>0.5</td>
</tr>
<tr>
<td>- atrial fibrillation</td>
<td>5 (10%)</td>
<td>13 (11.4%)</td>
<td>0.3</td>
</tr>
<tr>
<td>- DCM</td>
<td>1 (2%)</td>
<td>4 (3.5%)</td>
<td>0.3</td>
</tr>
<tr>
<td>- pe</td>
<td>2 (4%)</td>
<td>3 (2.6%)</td>
<td>0.5</td>
</tr>
</tbody>
</table>

Bridging group: patients receiving LMWH + VKA; Control group: patients receiving VKA only: n: number of tests; BMI: body mass index; Wc : white blood cells; Crp : C-reactive protein; DCM : dilated cardiomyopathy; PE : pulmonary embolus; Vka: vitamin-K-antagonist, LMWH : low molecular weight heparin.
Table 2
Dual INR values in the two groups.

<table>
<thead>
<tr>
<th></th>
<th>Bridging group (n = 50)</th>
<th>Control group (n = 114)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean INR&lt;sub&gt;lab&lt;/sub&gt;</td>
<td>1.89 ± 0.45</td>
<td>2.75 ± 1.00</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Mean INR&lt;sub&gt;P&lt;/sub&gt;</td>
<td>1.81 ± 0.50</td>
<td>2.44 ± 0.99</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>INR&lt;sub&gt;lab&lt;/sub&gt; – INR&lt;sub&gt;P&lt;/sub&gt; (absolute value)</td>
<td>0.09 ± 0.38</td>
<td>0.30 ± 0.51</td>
<td>0.01</td>
</tr>
<tr>
<td>INR&lt;sub&gt;lab&lt;/sub&gt; – INR&lt;sub&gt;P&lt;/sub&gt; (absolute value)</td>
<td>4 ± 7%</td>
<td>10 ± 14%</td>
<td>0.02</td>
</tr>
<tr>
<td>Dual measurement within 0.5 INR units</td>
<td>94%</td>
<td>80%</td>
<td>0.02</td>
</tr>
</tbody>
</table>

For all dual INR measurements, 94% were within 0.5 INR-units in the bridging group and 80% in the control group (p = 0.02) (Table 2).

Simple regression analysis revealed only three parameters significantly correlated with the RMD: haemoglobinemia (p = 0.006), LMWH administration (p = 0.05) and lab INR (p = 0.002).

By multivariate analysis, INR lab was the only factor correlated with the RMD (Table 3). As well, because mean INR was higher in the control group than in the bridging group, mean difference in INR value (INR<sub>lab</sub> – INR<sub>P</sub>) between the groups was statistically significant: 0.30 ± 0.51 in the control group versus 0.09 ± 0.38 in the bridging group (p = 0.01).

Global AC was of 74% in the bridging group and 70% in the control group (Table 4).

AC decreased with increasing INR: for INR < 2.0, AC was of 89.1%; for 2 ≤ INR < 3.0, AC = 72.2%; for 3.0 ≤ INR < 4.0, AC = 40% and for 4.0 ≤ INR, AC = 38%.

Finally, in assessing the clinical relevance of discordance INR values, the number of instances when a discordant INR value would have changed a clinical decision was similar in the bridging (n = 5/50 = 10%) and control groups (n = 9/114 = 7.9%; p = 0.6).

Discussion

The results of this first prospective study are suggesting that LMWH administration during bridging to achieve optimal INR does not modify the reliability of the POC monitor used to determine the INR in patients receiving a VKA treatment.

POC devices have been widely shown to have efficiency, accuracy and usefulness in patients with stable disease receiving VKA for a long time [1,2]; in this setting, these portable monitors are used by the patients for self-INR measurement with or without self-management of the VKA treatment.

However, the monitors could also be used for non stable patients, and in particular for those receiving a VKA and a LMWH simultaneously until the target INR is reached.

This situation is frequent at the beginning of the VKA treatment or when it has been temporarily stopped for an extracardiac surgery. During this LMWH/VKA bridging period, INR measurements are more frequent (than in stable patients) and need to be accurate because hemorrhagic and thromboembolic risks are higher. Therefore, the use of a POC, by permitting more frequent INR measurements, could help reduce these risks.

However, when comparing a whole blood finger prick (INR<sub>P</sub>) measurement to that from a plasma based laboratory system (INR<sub>lab</sub>), several factors can classically modify the results of the POC: antiphospholipid antibodies, low hematocrit level and heparin administration [3,4,7]. In particular, LMWH administration was suspected to increase the rate of discordance between INR<sub>P</sub> and INR<sub>lab</sub> in a small retrospective study conducted with another POC monitor (CoaguChek®) [3].
In this study we prospectively investigated the accuracy of an \textit{INR}_{POC} monitor as compared with the conventional laboratory method to measure \textit{INR} in patients receiving VKA and LMWH. Using \textit{INR}_{lab} as a reference, we compared the efficiency of the POC in the bridging and control groups by several tests.

It must be emphasized that, from a clinical point of view, it is difficult to affirm that two tests have a similar accuracy; in deed, an excellent result on average must not hide one or two aberrant results that could lead to an inappropriate clinical decision (such as for instance increasing the VKA dose when it should be decreased or temporarily stopped). Moreover, even if we considered \textit{INR}_{lab} as the reference, determining which of the two values is the right one is difficult when a discordance exists between the two measures. Some arguments favor the POC measurement: absence of delay between puncture and dosage, no need to transport blood sample test tubes and presence of two quality control channels on each strip.

Firstly, we used a simple linear regression to determine accuracy (Fig. 1) because it seems to be a standard approach to compare POC and laboratory \textit{INR} values [3-5]: the results were good: correlation coefficients between \textit{INR}_{POC} and \textit{INR}_{lab} values for the bridging group and the control group were of 0.81 and 0.87 respectively. However, this analysis alone is insufficient. Indeed, linear correlation is a measure of the degree of linearity between two variables; as long as the relationship is linear, even if one variable is consistently higher than the other, there will be a high degree of correlation. For instance, when calculating the kappa coefficients (which evaluate the concordance between two judgments), we found that the two tests were not interchangeable because kappa coefficients were weak in the two groups (kappa = 0.30 in the control group and 0.35 in the bridging group).

However, the kappa value was not modified by LMWH administration, and all the other tests that evaluated the concordance between the two methods of measure (AC calculation, RMD calculation, dual measurements within 0.5 \textit{INR} units, clinical discordance) suggest that LMWH administration does not modify the relationship between \textit{INR}_{POC} and \textit{INR}_{lab}.

The only parameter correlated with the divergence between the two \textit{INR} measurement methods was the magnitude of the \textit{INR}_{lab} : the higher the \textit{INR}, the higher the divergence.

Another interesting finding was that the rate of test strip failure was very high (29%) in the bridging group while it was in keeping with what is usually observed [8] (4%) in the control group. This result could not been explained by the manufacturer and must be confirmed in other studies before being admitted.

Our findings suggest that POC can be used to determine \textit{INR} in patients receiving LMWH as a bridging treatment; indeed, the device gives either a result, which is as reliable as for patients not receiving LMWH, or (in 29% of the cases), the machine fails to give a result, with no increase of misleading results.

The present study has some limitations. Three POC monitors are currently available worldwide: these are the Coaguchek®, the protime monitor (ITC), and the INRatio® (Hemosens). Only the last one has recently been made available in France, which is why it was used in our study. Therefore, our results are true only for the INRatio® POC. Secondly, there were few high \textit{INRs} in the bridging group; this was due to the fact that LMWH administration was stopped when the target \textit{INR} was reached. Finally, cardiac surgery patients made up the vast majority of the bridging group; therefore, one must be careful generalizing the results reported here to patients who are starting VKA with LMWH overlap but have not undergone recent cardiothoracic surgery.

In conclusion, the correlation between the \textit{INR} measurements determined by the classical reference laboratory method and the INRatio® portable INR monitor in patients receiving VKA is not perfect but is clinically acceptable and similar to the correlation observed by using other POC monitors. Co-administration of LMWH decreases the rate of successful measurements but does not modify this correlation. The only parameter correlated with the divergence between the two measures is the magnitude of \textit{INR}.

In summary, when the device gives a result, it is as accurate whether the patient receives a LMWH or not. Therefore, such \textit{INR} measurement could be useful not only for long term anticoagulated patients, but also during the high thromboembolic and haemorrhagic risk period of LMWH/VKA bridging, when \textit{INR} measurements should be made frequently. However, as the study was small and used only one POC instrument, its results should be interpreted with caution until it can be repeated.

References