Limits of agreement between measures obtained from standard laboratory and the point-of-care device Hemochron Signature Elite® during acute haemorrhage

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Editor’s key points

- Point-of-care testing devices are increasingly useful, but their accuracy in clinical practice is not fully determined.
- This study compared the accuracy of the Hemochron Signature Elite® with standard laboratory testing during acute haemorrhage.
- The Hemochron Signature Elite® showed only moderate agreement with laboratory values, and limits of agreement were wide.
- These data suggest that this device should not be used to diagnose coagulopathy and guide treatment in acute haemorrhage.

Background. Rapid diagnosis of coagulopathy in the bleeding patient using point-of-care (POC) devices would be ideal. The Hemochron Signature Elite® (HC®) is a POC device that determines international normalized ratio (INR) and activated partial thromboplastin time (aPTT). The aim of the study was to evaluate the agreement for INR and aPTT between the HC® and standard laboratory values in acute haemorrhage.

Methods. This was a single-centre observational prospective study including patients with acute haemorrhage. Laboratory INR and aPTT were compared with simultaneous measurements performed with the HC®. The diagnostic performance of HC® was determined; bias and limits of agreement were calculated according to the method of Bland and Altman.

Results. Seventy-two pairs of measurements from 39 patients were analysed. The bias between the INR-HC® and aPTT-HC® measurements and the central laboratory were 0.02 and 2.13, respectively. The Spearman’s correlation coefficients for the INR-HC®/INR-lab and the aPTT-HC®/aPTT-lab were 0.68 and 0.29, respectively. Twenty-seven per cent of INR-HC® values and 89% of the aPTT-HC® values exceeded the predefined limits of agreement. The INR-HC® measurement identified patients with a central laboratory INR > 1.5 with a sensitivity, specificity, and positive and negative predictive values of 83%, 70%, 76%, and 77%, respectively.

Conclusions. The results showed a lack of agreement between the INR-HC® and the aPTT-HC® measurements and the standard laboratory in the context of acute haemorrhage. The INR-HC® showed moderate performance as a decision-making tool to detect coagulopathy in the context of acute haemorrhage.

Keywords: blood coagulation disorders; haemorrhage; injuries; point-of-care systems; surgical blood loss

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of the measurements are contradicting. This can be partly explained by the heterogeneous setting of the existing studies. These settings differ from acute haemorrhage for pharmacological and physiological reasons such as use of anticoagulants, activation of procoagulatory cascades induced by the extracorporeal circulation on the one side and a systemic inflammatory response, haemodilution, and acidosis on the other. Consequently, measurements performed in the setting of acute haemorrhage are likely to differ. Few evaluations have been performed in the setting of haemorrhage and none for the Hemochron Signature Elite® (HC®). For these reasons, it appeared necessary to evaluate this device for its reliability and validity in the context of acute haemorrhage before integration into a management algorithm.

The aim of this study was to determine the limits of agreement between the prothrombin time/international normalized ratio (PT/INR) and activated partial thromboplastin time (aPTT) measurements by the POC device Hemochron Signature Elite® (HC®) and the corresponding measurements provided by a central laboratory in the context of acute haemorrhage.

Methods

Study design

This was a single-centre prospective observational study that took place in a trauma centre in the North of Paris between February and August 2011. The institutional review board gave its approval (CEERB no. 11-024) and waived the need for written informed consent.

Acute haemorrhage was defined as a transfusion requirement exceeding four red blood cell (RBC) concentrates in the first 6 h of acute haemorrhage, a systolic arterial pressure < 90 mm Hg, or both attributable to acute haemorrhage. Not all measurements were performed after transfusion of four RBC concentrates, in particular if the haemorrhage was likely to continue.

The haemodynamic and transfusion management of the patients in acute haemorrhage was left completely to the discretion of the physician in charge, on the basis of the most recent European recommendations. The results of the POC measurement were never disclosed to the physician in charge. Every included patient was supposed to be measured as long as the coagulopathy was still ongoing (INR > 1.2), but no more than three pairs were considered for analysis.

Patients with known coagulation disorders, post-partum haemorrhage, or advanced liver disease such as Child–Pugh score ≥ B were not included, since the underlying physiological and pathophysiological mechanisms of coagulopathy were considered as potential confounders.

A cut-off of INR > 1.5 and aPTT × 1.5 in the laboratory measurement were chosen to define coagulopathy and analyse the diagnostic accuracy of the HC® device. Three additional cut-offs for INR (>2.0, >2.5, >3) and aPTT (×2, ×2.5, ×3) were arbitrarily chosen to facilitate the comparison for higher values.

Preanalytical steps

Blood samples for measurement with the HC® and the central laboratory tests were always drawn simultaneously either through a non-heparinised arterial catheter or a central venous catheter or a peripheral venous puncture. If the sample was drawn on a catheter, the first 10 ml was always discarded. Capillary blood was never used. The samples for the central laboratory were collected into citrated vacutainer tubes (0.129 M) (Beckton Dickinson). On arrival at the central laboratory, the blood was centrifuged for 15 min at 2500 g at 20°C.

Description of the POC device and POC measurement

The HC® [International Technidyne Corporation (ITC), Edison, NJ, USA] is a portable coagulation device designed to perform near-patient measurement of whole blood ‘equivalent’ of various clotting times such as PT/INR and aPTT. Non-anticoagulated whole blood (25 μl for PT and 45 μl for aPTT) is disposed in the well of a specific 37°C prewarmed single-use cartridge. Each cartridge holds the necessary reagents for the specific test. Once the blood is disposed on the cartridge, the instrument aspirates the required amount of blood into the analysis chamber. The remainder of the blood is isolated from the chamber and discarded. After mixing with the reagents, the sample is then exposed to optical detectors. The formation of a clot is indicated to the detectors by a slowing of the flow in the chamber. An internal chronometer linked to the detectors measures the time required to form the clot. The HC® cartridges for aPTT (aPTT-HC®) use phospholipids and kaolin as activators. The result is given in seconds for the whole blood and plasma equivalent. According to the manufacturer, the HC® cartridges for INR (INR-HC®) are supposed to be sensitive for factors II, V, VII, and X and for fibrinogen. The thromboplastin of rabbit origin in the cartridges is a very sensitive reagent, with an International Sensibility Index (ISI) around 1. The assay exists for whole and citrated blood. In this study, the whole blood assay was used. The plasma equivalent is determined from an INR based upon an ISI of 1. In contrast to the standard procedure, the HC® calculates the INR directly from the sample to reduce mathematical imprecision resulting from intermediary steps (according to the manufacturer). The results are given in INR. For the HC® measurements, a decrease in the sampled whole blood from a syringe was disposed in a prewarmed single-use cartridge specific for INR and aPTT. The same lot of INR and aPTT cartridges was used throughout the study. Regular electronic quality control using electronic cartridges and a true biological quality control using lyophilized whole blood controls were carried out in accordance with the recommendations of the supplier in France (Laboratoire Gamida, ZA des Alouettes, Eaubonne, France). The device considers INR and aPTT measurements alike as out of detection range when they exceed 90–287 s for whole blood and 20.0–396.9 s for plasma-equivalent. A trained nurse realized all POC measurements.

Description of the laboratory assays

Central laboratory measurements for PT were realized with the reagent Thromborel S®, a thromboplastin of human origin with an ISI of 1.06 on the coagulation analysis system BCS-XP (Siemens Healthcare Diagnostics, Germany). An INR was then
calculated according to international standards. The INR laboratory sample was out of detection range up to a limit of 150 s.

The aPTT measurement was realized in the same aforementioned Siemens coagulation analysis system with the reagent TriniCLOT® Automated aPTT (Trinity Biotech, USA). The aPTT laboratory sample was out of detection range up to a limit of 170 s and a patient-to-control ratio > 5.

**Clinical and biological data**

All collected biological and clinical parameters were predetermined. Biological parameters were sampled at the same time as the coagulation and HC® samples and consisted of complete blood count, fibrinogen, lactate, blood gas analysis, and calcium concentration. Clinical and epidemiological data, such as the amount of required blood products such as packed RBCs, fresh-frozen plasma (FFP), platelets, arterial pressure, heart rate, etc., were noted concomitantly for all blood samples. The clinical severity scores, including the Simplified Acute Physiology Score (SAPS II), Injury Severity Score (ISS), and Sequential Organ Failure (SOFA), were calculated after 24 h by physicians blinded to the HC® results.

**Statistical analysis**

Data are presented as the median (25th - 75th percentile) for continuous variables and frequency (%) for qualitative variables. The Kolmogorov–Smirnov test was used to assess whether continuous data were normally distributed. The interdependence of HC® measurement with clinical data, biological data, and severity scores was evaluated using the non-parametric Spearman’s correlation coefficient (r) due to the skewed variable’s distribution and outlier’s presence. Given the results of previous studies in non-haemorrhagic conditions, Spearman’s correlation coefficient was calculated for the INR-HC®/INR-lab and the aPTT-HC®/aPTT-lab.15–17 21 The bias was calculated according to the Bland–Altman method for repeated measurements22 23 and measurements for the same patient were limited to three. There is currently not a consensual definition of an acceptable bias for PT or aPTT POC measurements in comparison with a central laboratory. Consequently we decided to consider that the agreement was clinically pertinent and acceptable if < 5% of HC® measurements were 20% higher or lower than the corresponding laboratory values.15 The limits of agreement between HC® and central laboratory test results according to the Bland–Altman method are given as well (bias (1.96 SD)). All tests were two-sided at the 0.05 significance level. All analyses were performed using R software version 2.15 (The R Foundation for Statistical Computing, Vienna, Austria).

**Results**

Over a period of 6 months from January to July 2011, 57 patients with acute haemorrhage were screened and 51 were tested (Fig. 1 and Table 1). Haemorrhage was a consequence of major trauma in 80% of patients, orthopaedic procedures in 15%, and miscellaneous reasons in 5%. Twelve (13%) pairs of comparisons were discarded because of invalid measurements either because the aPTT-HC®, INR-HC® measurements, and/or corresponding laboratory values were out of range or data were missing. These measurements corresponded to six very severely injured patients in overt shock.

Table 1  Patient characteristics (n=39). Data are presented as absolute (%), mean for age (range), and median (interquartile range) for all other variables

<table>
<thead>
<tr>
<th>Variables</th>
<th>All patients (n=39)</th>
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<tbody>
<tr>
<td>Male gender</td>
<td>25 (64%)</td>
</tr>
<tr>
<td>Age (yr)</td>
<td>45 (16, 88)</td>
</tr>
<tr>
<td>Systolic arterial pressure (mm Hg)</td>
<td>100 (88, 120)</td>
</tr>
<tr>
<td>Heart rate (beats min⁻¹)</td>
<td>112 (91, 120)</td>
</tr>
<tr>
<td>Lactate (mmol litre⁻¹)</td>
<td>3.29 (2.2, 6.31)</td>
</tr>
<tr>
<td>pH</td>
<td>7.28 (7.16, 7.33)</td>
</tr>
<tr>
<td>Hb (g litre⁻¹)</td>
<td>91 (72, 104)</td>
</tr>
<tr>
<td>Temperature (°C)</td>
<td>35.6 (35, 36.8)</td>
</tr>
<tr>
<td>Platelets (10³ μl⁻¹)</td>
<td>119 (82, 184)</td>
</tr>
<tr>
<td>Fibrinogen (g litre⁻¹)</td>
<td>1.65 (1.02, 2.22)</td>
</tr>
<tr>
<td>Laboratory INR</td>
<td>1.55 (1.33, 1.78)</td>
</tr>
<tr>
<td>Laboratory aPTT (patient-to-control ratio)</td>
<td>1.22 (1.02, 1.69)</td>
</tr>
<tr>
<td>INR-HC&lt;sup&gt;®&lt;/sup&gt;</td>
<td>1.50 (1.30, 1.83)</td>
</tr>
<tr>
<td>aPTT-HC&lt;sup&gt;®&lt;/sup&gt; (patient-to-control ratio)</td>
<td>2.37 (2.2, 2.55)</td>
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</tbody>
</table>

Consequently 39 patients and 73 pairs of measurements were studied. Fifteen patients were measured once, because they died before the second measurement or because of technical problems, 14 patients were measured twice, and 10 patients were measured three times. After exclusion of invalid or missing data, 68 pairs of comparison for INR-HC<sup>®</sup> and 65 pairs for aPTT-HC<sup>®</sup> were finally analysed.

The median time to obtain HC<sup>®</sup> results did not exceed 5 min; the median time for laboratory results was 43 min (26, 60). The median blood products requirements in the first 6 h were 4 (2, 5) RBC concentrates, 3 (0, 4) FFP, and 0 (0, 1) platelets.

The INR-HC<sup>®</sup> measurements were out of the predefined clinically pertinent agreement with the value determined in the central laboratory in 27% (19/68). The aPTT-HC<sup>®</sup> results were out of agreement for 89% (58/65) of the measurements.

The bias between the INR-HC<sup>®</sup> measurements and the central laboratory values was −0.02 with an upper limit of agreement of +0.87 (mean ± 2 SD) and a lower limit of −0.94 (mean − 2 SD). The bias for the aPTT-HC<sup>®</sup> measurement between the HC<sup>®</sup> and the central laboratory was −1.13, with an upper limit of agreement of +0.09 (mean ± 2 SD) and a lower limit of −2.35 (mean − 2 SD). Of INR-HC<sup>®</sup> values, 5.8% (4/68), and 42% (27/65) of the aPTT-HC<sup>®</sup> values, exceeded the upper or lower limits of agreement determined with the Bland–Altman method (Figs 2 and 3). The Spearman’s correlation coefficients were 0.68 for the correlation between INR-HC<sup>®</sup>/INR-lab and −0.29 for the correlation between aPTT-HC<sup>®</sup>/aPTT-lab.

With regard to the diagnostic accuracy of the device, because of the observed low level of agreement, data about the aPTT-HC<sup>®</sup> measurements were not analysed. The predictive performance of the INR-HC<sup>®</sup> measurement to accurately diagnose an INR > 1.5, >2, >2.5, and >3 is displayed in Table 2. Considering that an INR > 1.5 would trigger FFP administration in acute haemorrhage, the values from the central laboratory would suggest an FFP administration in 11% (8/68) of measurements, whereas the INR-HC<sup>®</sup> measurements would not. On the contrary, in 19% (13/68), the INR-HC<sup>®</sup> would suggest FFP administration, whereas INR laboratory values were <1.5.

The highest correlation for INR-HC<sup>®</sup> with other clinical or biological parameters was achieved with blood lactate concentration (r=0.4), body temperature (r=−0.41), and haemoglobin
concentration \((r = -0.32)\). For aPTT-HC\textsuperscript{w} measurements, correlation was equally low. All other parameters, including heart rate, systolic arterial pressure, fibrinogen concentration, platelet count, haematocrit, and calcium, showed no correlation. The same was true for the ISS, SOFA, and SAPS II scores.

**Discussion**

To our knowledge, this is the first study to evaluate the agreement and diagnostic performance of INR-HC\textsuperscript{w} and aPTT-HC\textsuperscript{w} measurements in the context of acute haemorrhage. In this very specific setting, the results demonstrated that 27\% of INR-HC\textsuperscript{w} measurements were out of the predefined range of clinically relevant agreement, with a bias between the INR-HC\textsuperscript{w} measurements and the central laboratory values of \(-0.02\) and a correlation coefficient of 0.68. Five per cent of INR-HC\textsuperscript{w} values exceeded the limits of agreement. The aPTT-HC\textsuperscript{w} measurements were out of the limits of agreement in 89\% and showed a more important bias of \(-1.13\) and a correlation of \(-0.29\). Concordantly, both methods did not meet the requirements for concordance with the central laboratory values, neither for the clinical nor the standard statistical agreement definitions.

Methodological factors could probably contribute to the general lack of agreement between HC\textsuperscript{w} measurements and laboratory values. The HC\textsuperscript{w} system uses whole blood and is calibrated for normal haematocrit and platelet counts, whereas the laboratory uses plasma. During haemorrhage, major fluctuations of haematocrit or platelet counts occur and are susceptible to alter POC measurements.\textsuperscript{18} In the central laboratory, the use of platelet-depleted plasma through centrifugation and processing for INR and aPTT measurements decreases interindividual differences related to platelet count variation. These variations in preanalytical technique may account for important variations between the two techniques.

Moreover, the particularly low agreement between the aPTT-HC\textsuperscript{w} and the central laboratory is also probably associated with the fact that the former is, in contrast to the latter, a Kaolin-based assay. This has already been suggested in another study in the context of heparin therapy monitoring for vascular surgery.\textsuperscript{24}

The moderate agreement for the INR-HC\textsuperscript{w} is more surprising since the measurement is based on a thromboplastin with an ISI close to one, similar to the one used in our central laboratory. Noteworthy, the moderate agreement tended to weaken with higher INR values \(>2\). This observation is in accordance with other studies and with other devices, although they have been realized in a different context such as oral anticoagulation monitoring,\textsuperscript{15–17} liver transplantation,\textsuperscript{21} and cardiac surgery.\textsuperscript{25} However, it appears difficult to provide a satisfying explanation for this phenomenon.

Besides preanalytical or analytical considerations, the particular setting of acute haemorrhage may account for the lack of agreement. Indeed, acute haemorrhage is associated with an inflammatory response that activates complex coagulopathic pathways. Moreover, fluid loading and macromolecules modify the blood of resuscitated patients. Both factors likely affect the precision and reliability of the assay. Generally, aPTT assays seem more easily influenced by these factors. The influence of these factors increases as the coagulopathy intensifies, which may decrease the reliability of the system. This could explain why we observed a much lower agreement for higher INR values. Similarly, the observation that all HC\textsuperscript{w} measurements were significantly more often out of range or unusable during severe coagulopathy in the most unstable and severely bleeding patients substantiates this assumption. The two outliers in Figure 2 appear as an exception. But it is noteworthy that both measurements correspond to patients in severe haemorrhagic shock coagulopathy and that the laboratory and POC values were highly concordant.

It should be noted that the HC\textsuperscript{w} device was developed for oral anticoagulation monitoring. Agreement in this very specific context appears often not acceptable.\textsuperscript{26} One study reported an overall bias of \(-3.6\%\) and a coefficient of variation of 8.4\%, with 16\% of measurements exceeding the 20\% margin of error.\textsuperscript{15} In another work, the use of a correction factor was required to reduce the bias.\textsuperscript{17} A more recent publication observed an overestimation of INR values \(<3\) and underestimation of values \(>4\), which was associated with a clinical therapeutic impact in 31\% of cases.\textsuperscript{26}

Against other POC devices that have been tested in acute haemorrhage,\textsuperscript{11, 18, 26} the HC\textsuperscript{w} compares unfavourably. In these studies, agreement for the INR-POC measurement was within acceptable limits, but tended to weaken in more severe coagulopathy with higher INR values according to the Bland–Altman analysis. Agreement for aPTT-POC measurements was tested in one study and agreement was found to be unacceptable for clinical purposes.\textsuperscript{11} A more recent study demonstrated a very satisfying agreement between another POC device to determine INR and a considerable acceleration of the amount of time to initiate haemostatic resuscitation compared with the central laboratory.\textsuperscript{19}

In the context of acute haemorrhage, patients with shock associated with massive blood loss and coagulopathy are easily detected by clinical judgement and heuristics alone,\textsuperscript{10} and appropriate blood component therapy is rapidly initiated. In contrast, moderately severe patients do not necessarily present with such an obvious picture of shock and overt coagulopathy. In this context, a POC device could accelerate the recognition of an ongoing coagulopathy. The INR-HC\textsuperscript{w} measurement would have identified patients with an INR \(>1.5\) with a sensitivity of 83\%. This corresponds to a positive predictive value of 76\%. However, these results were obtained after discarding a considerable number of measurements provided by the HC\textsuperscript{w} as ‘out of range’. This leaves only a small window of precision for the HC\textsuperscript{w} to provide the clinician with reliable clinical information. More sophisticated visco-elastic POC devices (like TEG or ROTEM) offer the advantage of a better characterization of the coagulopathy and appear to be more sensitive and specific with regard to detecting hyperfibrinolysis.\textsuperscript{27} But their clinical relevance, apart from promising results in the context of cardiac surgery,\textsuperscript{18} still awaits validation to guide blood transfusion. Moreover, viscoelastic POC (such as ROTEM or TEG) devices require the development of a specific competence in order to
perform and interpret the tests. Performing the individual test is more time-consuming than simpler POC devices such as the HC® and can take up to 10 min. This makes viscoelastic POC systems potentially less user friendly.

Limitations of this study need to be addressed. First, its single-centre character could lead to a selection bias. However, this increases the internal validity of the study. The second limitation is the repetitive testing of several patients. We tried to compensate for this by applying the modified Bland–Altman method for repetitive testing. Owing to the exclusion of invalid measurements, we cannot exclude that the study may be underpowered, in particular for samples with a high INR. Furthermore, from an analytical point of view, it would have been useful to compare the aPTT-HC® measurement with a laboratory assay that uses kaolin as the activator, whereas most routine aPTT measurements use micronized silica. The Bland–Altman plot in Figure 2 shows two outliers with very high INR. It should be noticed that these measurements belong to two patients in severe haemorrhagic shock and trauma-induced coagulopathy. Although the values appear elevated, both measures were kept in the analysis, because the POC and laboratory values were highly concordant and in accordance with the clinical situation. The suppression would lower the overall bias for the INR measurement, but still, >6% according to the HC® would be out of the limits of agreement according to the Bland–Altman method.

Finally, from a conceptual point of view, the study attempts to determine the agreement between two measurements; for this reason, the Bland–Altman method was used. This approach does not necessarily imply the superiority of one method over another. In fact, the central laboratory measurements of INR and aPTT have never been demonstrated stricto sensu to be a gold standard, especially in acute coagulopathy, but remain the available reference for the time being. Any alternative method therefore needs to compare with this reference. Finally, because there is currently no consensus definition, we used an arbitrary definition of acute haemorrhage, based on usual clinical parameters. The descriptive parameters of the included patients confirm that they were all acutely bleeding patients.

In conclusion, in the context of acute haemorrhage, a comparison between central laboratory and INR-HC® and aPTT-HC® measurements showed both a lack of agreement and insufficient precision. For this reason we cannot currently recommend its bedside use to diagnose coagulopathy in patients with acute haemorrhage. Furthermore, INR-HC® measurement shows only moderate performance as a decision-making tool to detect a coagulopathy defined by an INR >1.5. Although these results cannot be generalized to other POC tools, they highlight that new diagnostic tools require a thorough evaluation of their performance in the very specific context of their potential use.

Authors’ contributions

T.G. and S.H.: study design, data analysis, patient recruiting, and writing of manuscript; I.J.: data collection and patient recruiting; S.D.: data analysis and writing of manuscript; L.B.: technical advice writing of manuscript; J.M. writing of manuscript; C.P.-B.: study design and writing of manuscript.

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Declaration of interest

T.G. and S.H. were clinical investigators for the Beaujon of the Sangart–MPOX study. Both serve on the Expert Committee on Haemorrhagic Shock of the French Society of Anaesthesiology (SFAR). S.H. has also received funding for lectures and travel support from LFB. S.D. serves on the Expert Committee on Haemorrhagic Shock of the French Society of Anaesthesiology (SFAR). J.M. was the principal investigator for the Sangart MPOX trial at Beaujon and serves currently as editor for Anesthesiology and was the chief Editor of the Annales Francaises d’Anesthesie et de Reanimation from 2007 to 2011. C.P.-B. serves on the board of Liver Transplantation and has received funding for lectures and travel support from Astellas, MSD, and LFB.

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