RELEVANCE OF THE POINT-OF-CARE DEVICE HEMOCHRON SIGNATURE ELITE® IN PATIENTS WITH CIRRHOSIS DURING ORTHOTOPIC LIVER TRANSPLANTATION

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Abstract

Purpose: Real-time monitoring of hemostasis is believed to facilitate clinical care during surgery in some circumstances including orthotopic liver transplantation. The aim of this study was to compare International Normalized Ratio (INR) measurement by the point-of-care device Hemochron signature Elite® (HC) with the corresponding measurements provided by a central laboratory during orthotopic liver transplantation.

Methods: Patients undergoing orthotopic liver transplantation were included in this observational prospective study in two tertiary hospitals (Rennes, Toulouse) in France. Central laboratory and HC measurements of INR were assessed throughout the orthotopic liver transplantation. The agreement between the INR measurement by the POC device Hemochron Signature Elite® (HC) and the corresponding measurement provided by the central laboratory during liver transplantation was measured.

Results: Thirty patients (143 pairs of measurements) were analyzed. The median (25^{th}-75^{th} percentile) INR as assessed by the central laboratory was 1.83 (1.42-2.06). The correlation coefficient between the 2 methods was 0.76 ($P < 0.001$). The bias was 0.08 with an upper limit of agreement of +1.44 (mean +1.96 SD) and a lower limit of -1.29 (mean -1.96 SD). As INR increased, sensitivity decreased and was inferior to 50% when INR was >2.

Conclusion: HC cannot be recommended for routine management of orthotopic liver transplantation.

Keywords: cirrhosis, othotopic liver transplantation, point-of-care devices

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Implication statement: INR and its measurement by the point-of-care device Hemochron signature Elite® has been presented as a useful tool during OLT and is used by some clinicians. We report here that it is associated with a low sensitivity in cirrhotic patients and cannot be recommended for routine management of OLT.

Introduction

Rapid assessment of the International Normalized Ratio (INR) is believed to facilitate clinical care in some circumstances. A perfect tool would provide clinicians with 'real-time' accurate INR results enabling appropriate decisions. The point-of-care (POC) device Hemochron signature Elite® (HC) provides determination of INR. It was initially developed to monitor oral anticoagulation treatment[1] It was also evaluated during acute hemorrhage[2] and hemorrhagic surgery[3] with contradictory results. During orthotopic liver transplantation (OLT), two previous studies concluded with a partially good reliability of HC[4,5]. However, one study was retrospective, including few measurements[5] and both studies did not detail the cirrhotic status of the patients. This is of importance because INR cannot be interpreted identically in patients with or without cirrhosis. In patients with cirrhosis, blood coagulation is probably rebalanced towards normality because of the parallel reduction of procoagulant and anticoagulant factors[6]. Conventional coagulation tests probably do not reflect the whole coagulation or the risk of bleeding or thrombosis in these patients. During OLT, when patients have been transfused and diluted, hemostasis data are probably even more difficult to interpret. In contrast, INR is correlated with liver dysfunction in non-cirrhotic patients. Despite these contradictory observations, INR is widely used to calculate the patient's Model for End-Stage Liver Disease (MELD) score, which is used to prioritize candidates for liver transplantation. INR has also been presented as a useful tool to assess risk factors for bleeding during OLT[7]. Indeed, some clinicians are using HC during OLT to guide the transfusion. Our clinical experience with HC during OLT suggested that it was not accurate in cirrhotic patients. Therefore, before implementing HC during OLT to manage transfusion in our centers, we design a study to compare INR measurement by the point-of-care (POC) device Hemochron signature Elite® (HC) with the corresponding measurements provided by a central laboratory during OLT.

Patients and Methods

Study design

This prospective observational study was simultaneously conducted in two French university hospitals (Rennes and Toulouse) between January 2013 and January 2014. This study was performed according to the declaration of Helsinki. The institutional review board of the hospital (chairperson Dr Conil JM, University hospital of Toulouse, 1 avenue Jean Poulhès, 31059, Toulouse, France) gave its approval (registration n°39-0613) on July 2012. Blood tests used in this study are part of medical routine testing. Consent to participate in the study and consent to publish was orally obtained from each patient. Written informed consent was not required in accordance with French regulation.

The primary outcome tested was the agreement between the International Normalized Ratio (INR) measurement by the POC device Hemochron Signature Elite® (HC) and the corresponding measurement provided by the central laboratory during liver transplantation. All patients older than 18 years and undergoing liver transplantation were eligible. The absence of investigators was the only non-inclusion criteria. Management of the patients during liver transplantation was left completely to the discretion of the physician in charge. The physician was blind to the results of the POC. Both institutions› protocols for managing liver transplantation were similar and included biological parameter measurements 5 times during the surgery: 1) after surgical incision (T0), 2) after hepatectomy and before clamping the vena cava (T1), 3) after venous anastomosis and unclamping the vena cava (T2), 4) 30 minutes after unclamping the vena cava (T3), 5) at the end of surgery (T4). Blood samples

were drawn through a non-heparinized arterial catheter. Biological parameters included coagulation (PT, INR) and HC samples. The following data were recorded: sex, age, clinical severity scores (CHILD score, MELD score)[8], etiology of hepatic dysfunction and amount of blood products transfused.

POC Hemochron Signature Elite® measurements

HC device technology relies on the optical detection of clot formation. Blood samples were placed in cuvettes and loaded into the HC (Laboratoire Gamida, ZA des Alouettes, Eaubonne, France). Manufacturer instructions were followed as described on the package insert of the HC cuvette. Results were obtained in less than 5 minutes.

Laboratory assays

Whole blood was collected with 2.7mL 0.109M BD Vacutainer™ Plus Plastic Citrate Tubes (Le Pont de Claix, France) and was centrifuged at 2,500g for 15 minutes at 20°C at the central laboratory. PT/INR was determined using a STAR Evolution automaton and the thromboplastin reagent was an STA Neoplastin CI plus (ISI 1.28). All were supplied by Stago (Asnieres, France). Briefly, fifty microliters of plasma sample were incubated for 240 seconds at 37°C and mixed with one hundred microliters of calcium thromboplastin. Results from the central laboratory were obtained in approximately 45 minutes.

Statistical analysis

All statistical analyses were performed using SAS software ver. 9.3 (SAS Institute, Cary, NC). Data are presented as frequency (corresponding percentage) for qualitative variables and as mean ± SD or median (interquartile range (IQR)) in case of non-normality for continuous variables. Correlation between the two methods was estimated using the Spearman correlation coefficient. Agreement and bias were calculated according to the Bland-Altman method for repeated measurements[9]. For all analyses, a P value < 0.05 was considered as statistically significant.

Results

During the study period, 167 patients were screened and 30 were included in the study (Fig. 1). Demographics and transfusion data are shown in Tables 1 and 2. All patients had cirrhosis. Blood samples were obtained at the 5 predetermined times for all of the patients. Seven measurements were discarded for technical reasons. Consequently, 30 patients and 143 pairs of measurements were analyzed. The median INR measured by the central laboratory was 1.83 (IQR: 1.42-2.06). The correlation coefficient between the 2 methods was 0.76 ($P < 0.001$). The bias between the HC measurements and the central laboratory values was 0.08 with an upper limit of agreement of +1.44 (mean: + 1.96 SD) and a lower limit of -1.29 (mean: -1.96 SD) (Fig. 2). The predictive performance of the HC to detect an increased INR is displayed Table 3. As INR increased, sensitivity decreased and was inferior to 50% when INR was >2 in the whole population and in Child C patients.

Table 1
Patient characteristics

Number	30 patients
Gender (M/F)	27 (90%) / 3 (10%)
Age (year)	58 (55-61)
CHILD score:	
A	12 (40%)
B	6 (20%)
C	12 (40%)
MELD score	15 (10-20)
Etiology:	
Alcohol	23
Hepatitis C virus	6
Dysmetabolism	3
Acute hepatitis	1
Sclerosing cholangitis	1
Parasites	1
Primary biliary cirrhosis	1
Re transplantation	1
Hepatocarcinoma	9 (30%)
pH	7.32 (7.25-7.38)
Calcium (mmol.litre-1)	1.98 (1.81-2.13)
Fibrinogen (g.litre-1)	1.7 (1.48-2.27)
Hb (g.dlitre-1)	10.4 (9.4-12.4)
Platelets (G.litrel-1)	74 (49-106)
Factor V (UI.dlitre-1)	40 (30-52)
Laboratory INR	1.73 (1.4-2)
INR HC®	1.6 (1.4-1.8)

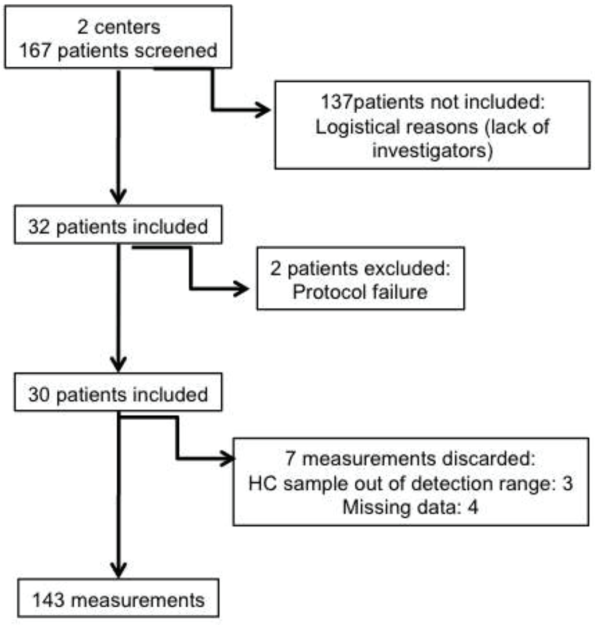
Data are presented as frequency (%) for qualitative variables, mean (range) for age, and median (25^{th}-75^{th} percentile) for the other continuous variables. Hb: hemoglobin, HC: hemochron.

Table 2
Transfusion data

RBC (units)	7.2 ± 5.4
FFP (units)	9.2 ± 5.8
Platelets (units)	1 ± 1.04

Data are presented as mean +/- SD. RBC units = red blood cells units, FFP = fresh frozen plasma.

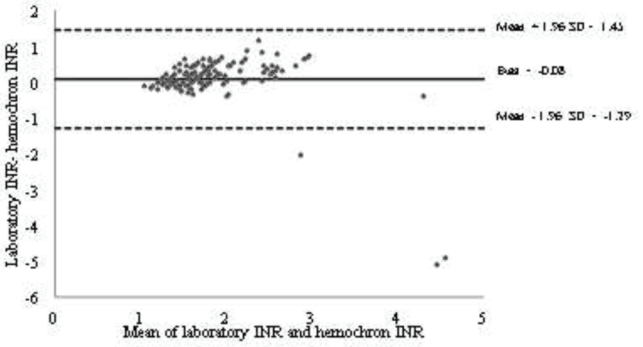
Fig. 1
Flow chart of patients



Discussion

Despite a statistically significant correlation in the measurements of INR by the central laboratory and by HC, as INR increased, sensitivity decreased. It was

Fig. 2
Bland-Altman diagram of the difference between the Hemochron INR and central laboratory INR measurements vs. the mean of the Hemochron INR and laboratory INR measurements.



inferior to 50% when INR was >2, indicating that HC is not accurate for routine management of orthotopic liver transplantation.

HC is calibrated for normal platelets and hemoglobin counts and uses whole blood to determine INR whereas laboratory assay uses plasma. Low platelets or hemoglobin could affect the results of HC. These methodological differences could explain our results. The lack of agreement between HC and laboratory assay is in accordance with previous studies realized in the context of acute hemorrhage[2] or cardiac surgery[10]. Only two previous studies have reported the use of HC in the context of OLT. Herbstreit et al. concluded with good agreement between laboratory assays and HC in measuring PT[4]. However, a look at the results in detail revealed a tendency towards

Table 3
Predictive performance of the INR-HC® measurement for clinical decision-making in the whole population and among Child C patients

	Sensitivity	**(%)**	**Specificity**	**(%)**	**PPV**	**(%)**	**NPV**	**(%)**
	All patients	Child C patients	All patients	Child C patients	All patients	Child C patients	All patients	Child C patients
INR > 1.5	74	78	78	44	88	88	59	27
INR > 2	44	52	97	91	86	80	80	74
INR > 2.5	25	40	98	94	63	57	89	88
INR > 3	20	25	98	94	25	25	97	94

PPV: positive predictive value, NPV: negative predictive value.

an underestimation of PT values in the range of 10-20s and an overestimation when PT values were higher than 30s[4]. This latter result, i.e. a discrepancy for high values, is similar to our results. A recent retrospective report[5] concluded with accuracy of HC prior to hepatic reperfusion. However, this latter study was retrospective, including fewer measurements per patient (only 3). Both studies did not detail the cirrhotic status of the patients. This is of importance because INR cannot be interpreted identically in patients with or without cirrhosis. In patients with cirrhosis, low PT and high INR are not necessary associated with increased bleeding[11]. These tests do not reflect the whole coagulation balance in these patients. The modern concept of rebalanced hemostatic status in cirrhosis[6] is now recognized as the most accurate. However, many decisions are still based on PT and INR in these patients[11]. Our results showed that in cirrhotic patients during OLT, HC was not reliable to evaluate INR. Rapid assessment of INR is then not available during OLT. Indeed, bleeding risk during OLT is thought to be multifactorial and not only due to the coagulopathy. Portal hypertension, endothelial dysfunction, bacterial infections, and renal failure could increase the risk of bleeding in cirrhosis[12].

Aside from using INR as an assessment of the coagulation status, it has been proposed to guide the transfusion during OLT. INR > 1.6 was shown to be a risk factor for massive transfusion bleeding during OLT[7]. In the later retrospective publication on HC during OLT, which reported accuracy of HC prior to hepatic reperfusion, plasma transfusion was recommended when INR was higher than 1.8[5]. Clinical experience and previous publications have shown that practices vary widely[13,14], mostly because decision of transfusion during OLT is not only based on biological parameters. Indeed, many other factors contribute to in bleeding risk during OLT[15]. The severity of the liver disease, the degree of portal hypertension, the renal failure, the acidosis, the hypothermia, the surgical difficulties and the appreciation of the operative field during the intervention are many factors helping in transfusion decision-making[16]. These factors are difficult to quantify and some clinicians deemed rapid assessment of PT or INR necessary. Careful clinical observation of blood loss would be more clinically meaningful than correction of coagulopathy and could lead to less fluid administration and therefore less transfusion[17,18]. Some authors have therefore proposed to cautiously use coagulation profile[17]. According to our results, HC measurement would have identified patients with an INR > 2 with a sensitivity of 44% and a positive predictive value of 86%. Moreover, some samples were discarded because they were defined as "out of range" by HC. Not only is the treatment of an abnormal coagulation profile a matter of debate, but there is also the precision of the tool. HC is not accurate enough to influence a decision for transfusion.

The main limitation of our study is the analysis of repetitive testing of several patients. We compensated for this limit by using the Bland-Altman method for repetitive testing[9].

In conclusion, comparison of laboratory and HC measurements showed a lack of agreement and precision. Contrary to the propositions of some manufacturers and clinicians, HC cannot be recommended for routine management of orthotopic liver transplantation.

Declarations section

List of abbreviation: International Normalized Ratio (INR), Hemochron signature Elite® (HC), point-of-care (POC), orthotopic liver transplantation (OLT), Model for End-Stage Liver Disease (MELD)

Ethics (and consent to participate): This study was performed according to the declaration of Helsinki. The institutional review board of the hospital (chairperson Dr Conil JM, University hospital of Toulouse, 1 avenue Jean Poulhès, 31059, Toulouse, France) gave its approval (registration n° 39 – 0613) on July 2012. Blood tests used in this study are part of medical routine testing. Consent to participate in the study and consent to publish was orally obtained from each patient. Written informed consent was not required in accordance with French regulation.

Competing interests: Funding sources were solely institutional. **Conflict of interest:** None

Authors' contributions: PG and SV carried out the HC calibration. HB, BB, VM and ED carried out the patients' inclusions. HB and VM conceived of the study, and participated in its design and coordination

and helped to draft the manuscript and performed the statistical analysis. All authors read and approved the final manuscript.

Availability of data and materials: The datasets generated during and/or analysed during the current study are not publicly available but are available from the corresponding author on reasonable request.

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