Reliability of a point-of-care device for international normalized ratio testing during the three surgical phases of orthotopic liver transplantation: a retrospective observational study

Fiabilité d'un dispositif au chevet de mesure du rapport international normalisé pendant les trois phases chirurgicales d'une transplantation orthotopique de foie: étude observationnelle rétrospective

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Abstract

Purpose To investigate the reliability of a point-of-care device, the HEMOCHRON[®] Jr. Signature, for measuring the international normalized ratio (INR) during the three surgical phases of liver transplantation.

Methods A retrospective review was performed on patients undergoing liver transplantation during July to December 2013. Thirty-one patients who had simultaneous laboratory and point-of-care INR readings from each phase of liver transplant surgery (paleohepatic, anhepatic, and neohepatic) were eligible for inclusion. Bland-Altman

analysis, Spearman's rank correlation, and four quadrant plots were used to compare INR results from the point-of-care device (pocINR) with those from the laboratory (labINR).

Results Based on the Bland-Altman analysis, mean biases (95% prediction interval) were 0.10 (0.03 to 0.17), 0.19 (0.12 to 0.27), and 0.21 (0.01 to 0.43) for the paleohepatic, anhepatic, and neohepatic phases, respectively. The pocINR device showed a systematic underestimation of the labINR. The Spearman's rank correlation coefficients (95% confidence interval [CI]) were: $P = 0.90$ (95% CI 0.80 to 0.95); $P = 0.92$ (95% CI 0.71 to 0.93); and $P = 0.71$ (95% CI 0.46 to 0.85), respectively. Direction-of-change analysis between the paleohepatic to anhepatic and the anhepatic to neohepatic phases showed strong concordance of 84% and, also considering the small bias between the measurements, supports the use of the pocINR device in the clinical management of liver transplant surgery.

Conclusion Point-of-care INR was accurate prior to hepatic reperfusion, but reliability decreased in the neohepatic phase.

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Résumé

Objectif Étudier la fiabilité d'un dispositif au chevet, l'HEMOCHRON[®] Jr. Signature, pour la mesure du rapport international normalisé (RIN) pendant les trois phases chirurgicales d'une transplantation hépatique.

Méthodes : Une analyse rétrospective a été menée sur des patients ayant subi une transplantation hépatique entre juillet et décembre 2013. Trente et un patients ayant des

résultats simultanés du RIN pour chaque phase d'une chirurgie de transplantation hépatique (paléohépatique, anhépatique et néohépatique) provenant d'un laboratoire et d'un dispositif au chevet ont pu être inclus. Une analyse de Bland-Altman, une corrélation des rangs de Spearman et des graphiques à quatre quadrants ont été utilisés pour comparer les résultats du RIN obtenus au moyen du dispositif au chevet (pocINR) de ceux obtenus en laboratoire (labINR).

Résultats Basés sur l'analyse de Bland-Altman, les biais moyens (intervalle de prédiction de 95 %) étaient de 0,10 (0,03 à 0,17), 0,19 (0,12 à 0,27) et 0,21 (0,01 à 0,43) pour les phases, respectivement, paléohépatiques, anhépatiques et néohépatiques. Le pocINR a été systématiquement sous-estimé par rapport au labINR. Les coefficients de la corrélation des rangs de Spearman (intervalle de confiance [IC] à 95 %) étaient, respectivement, les suivants : $P = 0,90$ (IC à 95 % : 0,80 à 0,95); $P = 0,92$ (IC à 95 % : 0,71 à 0,93); et $P = 0,71$ (IC à 95 % : 0,46 à 0,85). L'analyse de la direction du changement entre les phases paléohépatiques et anhépatiques, et entre les phases anhépatiques et néohépatiques a montré une forte concordance de 84 % et, compte tenu des petits biais entre les mesures, est compatible avec l'utilisation du dispositif de pocINR pour la gestion clinique d'une chirurgie de transplantation hépatique.

Conclusion Le RIN au chevet a été exact avant la reperfusion hépatique, mais sa fiabilité a diminué dans la phase néohépatique.

The coagulopathy encountered during liver transplantation is multifactorial and dynamic. Pre-existing impairment in hepatic synthetic function causes deficiencies in procoagulant and antifibrinolytic factors, resulting in a complex coagulopathy that is difficult to manage.^{1,2} During transplantation surgery, the situation is further compounded by large fluid shifts, acidosis, hemorrhage, hemodilution, hypocalcemia, and hypothermia and can change rapidly and profoundly during the paleohepatic, anhepatic, and neohepatic phases of surgery. A rapid assessment of coagulation status is required in order to optimize patient management.

Coagulation monitoring has traditionally centred on assessment of the prothrombin time (PT)/international normalized ratio (INR), activated prothrombin time (aPTT), fibrinogen concentration, and platelet count. These tests reflect hemostasis at a particular epoch during liver transplantation. Delays in processing and reporting tests, combined with the dynamic nature of hemostasis

during transplantation, make the application of this information less than ideal.

Point-of-care (POC) coagulation assays with short turnaround times may allow for better management of coagulation during liver transplantation. Point-of-care assays for INR (pocINR) with short turnaround times have been developed expressly for domiciliary management of oral anticoagulation^{3–5} and may therefore be useful in liver transplantation.¹ There is emerging evidence, however, that the performance of these devices may be reduced at times of severe physiological derangement^{6–9} such as encountered during liver transplantation.

Therefore, the objective of this study was to compare the reliability of the pocINR with the gold standard laboratory INR (labINR) during the three phases of orthotopic liver transplantation. This information will help to determine the device's clinical utility in liver transplantation and its applicability for inclusion in a POC-based patient blood management program.

Methods

Research Ethics Board approval was obtained in June 2014 for this retrospective cohort study, and the need for informed consent was waived.

Population

During July to December 2013, we conducted a quality assurance assessment of the pocINR device in liver transplant recipients following its introduction to the operating rooms at the Toronto General Hospital, University Health Network, ON, Canada. Patients from this study period were included in the analysis if data were available for labINR and pocINR from simultaneous blood samples drawn during all three surgical phases: paleohepatic, anhepatic and neohepatic.

During the study period, all transplants were managed according to a standardized institutional practice.¹⁰ All patients received an initial bolus of tranexamic acid 10 mg·kg⁻¹ followed by 10 mg·kg⁻¹·hr⁻¹ until hepatic artery reconstruction was complete unless contraindicated (e.g., history of thromboembolic complications, primary sclerosing cholangitis, primary biliary cirrhosis, malignancy). A cell salvage system was utilized in all cases except where the transplant was performed for malignancy. The transfusion triggers recommended in our liver transplant program for the actively bleeding patient include red blood cells for hemoglobin < 80 g·L⁻¹, plasma for an INR > 1.8, platelets (4 U) for a platelet count of

$< 80 \times 10^9 \cdot \text{L}^{-1}$, and cryoprecipitate 10 U for a fibrinogen of $< 1 \text{ g} \cdot \text{L}^{-1}$.

Coagulation assessments

Two samples were taken concurrently in each of the three surgical periods by blood sampling from a peripheral arterial cannula (patency maintained with pressurized heparin-free normal saline) at (i) the paleohepatic phase (after induction of anesthesia but before cross-clamping), (ii) the anhepatic phase (after cross-clamping of the inferior vena cava, portal vein, and hepatic artery), and (iii) the neohepatic phase (during the anastomoses of the hepatic artery and biliary system following hepatic graft reperfusion). One sample was sent to the laboratory for INR analysis using the STA-R® Evolution Expert Series (Diagnostica Stago Inc., Parsippany, NJ, USA), while the other was used for POC analysis with the HEMOCHRON® Jr. Signature device (International Technidyne Corporation, Edison, NJ, USA.) which determines INR from optical detection of clot formation below a predetermined level.⁷

Data analysis

Preoperative patient characteristics, including demographics (age, height, weight), comorbidities (cardiac, respiratory, renal, and endocrine), laboratory results, and intraoperative blood transfusions were recorded to describe the surgical population. Bland-Altman analysis, Spearman's rank correlation, and four quadrant plots were used to compare INR results from the POC device with those from the laboratory. Bland-Altman plots were used to determine if there is a systematic bias in the pocINR measurement when compared with the labINR. Limits of agreement reflect the 95% prediction interval for the sample calculation (for which a calculation of $2.04 \times$ standard deviation was used); these represent the range of values in which agreement between methods will lie for 95% of the sample.¹¹ The limits of agreement indicate how far apart the two INR measurements will be 95% of the time.¹²

Percentage error was calculated by dividing the limits of agreement by the mean value of the existing method (labINR).^{11,13} This gives a relative estimation of the error by comparing the proportion of the error with the magnitude of the clinical measurement taken with the established method.

The ability of the pocINR to estimate changes in the labINR when moving between phases was evaluated using four quadrant plots comparing change in labINR and change in pocINR between: (a) the paleohepatic and anhepatic phase and (b) the anhepatic and neohepatic

phase. Trending was assessed using direction-of-change analysis, with concordance expressed as a percentage of total data points. Concordance is a measure of the proportion of data points that fall within one of the two quadrants of agreement. Values that differ by very small increments may appear to reduce the concordance between two measurements. Critchley *et al.* used an exclusion zone around small differences between measurements to limit this effect on the measurement of concordance.¹⁴ For our analysis of the concordance between labINR and pocINR, we chose to use a clinically relevant figure of 0.3 INR points for the exclusion zone.

Statistical analysis was conducted using R statistics (R Foundation for Statistical Computing, Vienna, Austria,

Table 1 Liver transplantation cases – demographics, preoperative laboratory data, and intraoperative blood transfusion

Demographics	(n = 31)
Age (yr)	53 (12)
Sex (female)	11 (44%)
Height (cm)	170 (9)
Weight (kg)	76 (12)
<i>Hepatopathology</i>	
Hepatitis C	11 (35%)
Alcoholic liver disease	4 (13%)
Hepatitis B	2 (6%)
Non-alcoholic Steatohepatitis	0 (0%)
Primary biliary cirrhosis	0 (0%)
Primary sclerosing Cholangitis	4 (13%)
Fulminant hepatic failure	2 (6%)
Other	7 (23%)
<i>Preoperative Laboratory Values</i>	
Hemoglobin ($\text{g} \cdot \text{L}^{-1}$)	109 (22)
Platelets ($\times 10^9 \cdot \text{L}^{-1}$)	94 (67)
Sodium ($\text{mmol} \cdot \text{L}^{-1}$)	136 (6)
Potassium ($\text{mmol} \cdot \text{L}^{-1}$)	3.9 (0.6)
Chloride ($\text{mmol} \cdot \text{L}^{-1}$)	107 (6)
Creatinine ($\mu\text{mol} \cdot \text{L}^{-1}$)	143 (106)
INR	1.7 (0.8)
aPTT (s)	40 (9)
Fibrinogen ($\text{g} \cdot \text{L}^{-1}$)	2.4 (1.0)
Albumin ($\text{g} \cdot \text{L}^{-1}$)	22 (18)
<i>Intraoperative Blood Transfusion</i>	
Packed red blood cells (0–2 U)	12 (39%)
Packed red blood cells (> 5 U)	9 (29%)
Frozen plasma (U)	4 [1,8]
Platelets (U)	4 [0,8]

Mean (standard deviation), Median [interquartile range], or proportion (%) of total. INR = international normalized ratio; aPTT = activated partial thromboplastin time

Table 2 INR results across surgical phases: range, mean, and standard error

<i>n</i> = 31	Minimum	Maximum	Mean	SE
<i>Paleohepatic</i>				
Laboratory	1.07	2.75	1.64	0.08
POC	1.1	3	1.54	0.08
<i>Anhepatic</i>				
Laboratory	1.12	2.68	1.8	0.07
POC	1.1	2.5	1.61	0.06
<i>Neohepatic</i>				
Laboratory	1.57	4.1	2.22	0.09
POC	0.8	3.7	2.01	0.11

INR = international normalized ratio; POC = point-of-care; SE = standard error

2013) and Excel™ (Microsoft Canada, Toronto, ON, Canada).

Results

Data were analyzed from 31 patients, all of whom underwent orthotopic liver transplantation (Table 1). The population studied was similar to 38 patients who were excluded due to insufficient INR data (data available, but not presented).

Mean INR increased from the start of surgery to the end, and there was a broader range and standard deviation in the neohepatic period (Table 2). The INR ranged from 0.8–3.7 with 19 of 93 (20%) values > 2.5.

Bland-Altman analysis (labINR – pocINR) across all three time periods showed a systemic underestimation of labINR by pocINR (Table 3 and Fig. 1). Limits of agreement were broader for the neohepatic phase (± 1.20) than for the other two phases (paleohepatic, ± 0.39 ; and anhepatic, ± 0.42). Percentage error ($\pm 17\%$ for a sample size of 31) was similarly increased in the neohepatic phase (54%) compared with the paleohepatic (23%) and anhepatic (22%) phases.

Spearman's rank correlation coefficients (95% confidence interval [CI]) for the three groups were: paleohepatic $P = 0.90$ (95% CI 0.80 to 0.95), anhepatic $P = 0.92$ (95% CI 0.71 to 0.93), and neohepatic $P = 0.71$ (95% CI 0.46 to 0.85). Correlation plots show the presence of several significant outliers in the neohepatic phase – labINR vs pocINR: 2.32 vs 3.7; 3.05 vs 0.8; and 4.1 vs 2.6 (Fig. 2). The removal of data points showing a difference of >1.5 INR units shows a correlation coefficient equivalent to that of the paleo- and anhepatic phases ($P = 0.90$; 95% CI 0.70 to 0.97).

Table 3 Bland-Altman analyses for laboratory INR

	Paleohepatic	Anhepatic	Neohepatic
Bias	0.10 (0.03 to 0.17)	0.19 (0.12 to 0.27)	0.21 (0.01 to 0.43)
<i>Limits of agreement</i>			
Lower	−0.30 (−0.43 to −0.18)	−0.23 (−0.36 to −0.10)	−0.99 (−1.36 to −0.62)
Upper	0.48 (0.38 to 0.63)	0.61 (0.49 to 0.75)	1.42 (1.05 to 1.79)
Percentage error	23%	22%	54%

Point-of-care international normalized ratio (INR): mean bias (95% confidence interval), limits of agreement (95% confidence interval), and percentage error

Four quadrant plots showed strong concordance of 84% for both the paleohepatic-anhepatic and anhepatic-neohepatic changes (Fig. 3).

Discussion

There is a good relationship between pocINR and labINR in the liver transplant setting. This is supported by its small mean bias and strong positive correlation in the paleohepatic (bias = 0.10; $P = 0.90$) and anhepatic (bias = 0.19; $P = 0.92$) phases, confirming its utility during the earlier surgical stages of the procedure.

The predictive accuracy worsened during the neohepatic phase, with a mean bias ($\pm$ limits of agreement) of 0.21 (± 1.20). Three outliers in the data (10% of the data points) were largely responsible for the lower correlation coefficient for these data compared with that for the paleo- and anhepatic data. Given the translation of this research into the clinical setting, ill-informed interpretation of this particular result may lead to inappropriate transfusion decisions, especially if relying on POC devices without confirmatory laboratory results.

Previous studies have suggested a systematic deviation between POC and laboratory analyses in INRs > 3.5.^{15–17} As the trigger for intraoperative transfusion is usually at a lower INR level, this outcome is unlikely to be of relevance in a perioperative liver transplant population. Our study did not replicate this finding; however, relatively few (20%) INR readings in the labINR and pocINR groups were > 2.5.

Studies looking specifically at pocINR taken during times of hemorrhage both intraoperatively⁷ and in trauma⁸ scenarios have found weak correlations between pocINR and laboratory PT estimations. This may be analogous to the situation following neohepatic reperfusion where the sequelae of hyperfibrinolysis, hypothermia, hypocalcemia,

Figure 1 Bland-Altman Graphs – Mean of individual labINR and pocINR data points plotted against the difference (labINR – pocINR) between readings across three phases. Hashed line: mean bias; solid line: limits of agreement (95% prediction interval): a. paleohepatic b. anhepatic c. neohepatic. labINR = laboratory international normalized ratio, pocINR = point-of-care international normalized ratio

and the imbalance between pro- and anticoagulant factors are expected to be at their most unstable or severe. Nevertheless, samples taken during the earlier phases of the transplantation support the findings of Herbstreit *et al.* who found a strong positive correlation between pocINR and laboratory PT estimations ($r = 0.91$) using the same POC device in liver transplantation.¹⁵

The pocINR performed well at predicting the direction of change of labINR between the three critical phases of liver transplantation (Fig. 3). After accounting for random scatter about the zero point (by use of an exclusion zone), the POC device achieved 84% accuracy when compared

Figure 2 Correlation scatter plots with line of best fit: a. paleohepatic b. anhepatic c. neohepatic. P = Spearman's rank correlation coefficients (95% confidence interval). labINR = laboratory international normalized ratio; pocINR = point-of-care international normalized ratio

with labINR. The pocINR is a reliable tool with which to forecast a worsening coagulopathy and to initiate ordering or administration of blood products as appropriate. By convention, a correlation for a stand-alone device should be $> 90\%$, but since the POC is being used as an adjunct to the laboratory measure, it certainly retains clinical utility in the management of the liver transplantation surgery.¹⁴ Nevertheless, its cautious use, particularly in the neohepatic phase, is an important consideration.

The major strength of the current study is the analysis of pocINR performance across all three phases of liver transplantation. This assessment provides a robust clinical

Figure 3 Four quadrant plots for the change in INR between phases of liver transplantation surgery: a. paleohepatic to anhepatic change b. anhepatic to neohepatic change. labINR = laboratory international normalized ratio; pocINR = point-of-care international normalized ratio

guide as to the reliability of a given result at a particular phase in the surgical procedure and under dramatically different biochemical and physiological conditions. In addition, the direction-of-change analysis showing the performance of the device at forecasting the change in INR between phases allows prediction of labINR not only between phases but also potentially in response to intervention.

Important limitations of this study include its retrospective design and small sample size. We could not explore the reasons for discrepancies in the two measures by performing serial measurements in each time period. Also, having a larger sample size may have reduced the influence of the outliers on our results. It should be stressed that the sample size for this study was one of convenience as this was a quality assurance project.

Other limitations arise from the validity of the instruments used in this setting. The HEMOCHRON Jr. Signature is well validated in INR prolongation due to warfarin and the vitamin K antagonists^{4,5} where there are deficiencies of factors II, VII, IX, X, as well as proteins induced in the absence of vitamin K (which are thought to prolong the INR in their own right).⁸ Several factors, including antiphospholipid syndrome, heparinization, and use of oral anticoagulants, may cause over or underestimation of the results.^{18–21} In the liver transplant population specifically, endogenous heparinoids released in liver failure, residual exogenous heparin from the donor harvesting procedures, and the effects of recombinant tissue plasminogen activator (administered into the hepatic graft as part of some donation after cardiac death protocols) may be contributory to inaccuracies in the measures.^{1,22} The HEMOCHRON Jr. Signature utilizes light-emitting diode optical detectors to determine clot formation below a predetermined threshold. The anemia commonly seen during liver surgery may interfere with the optical density analysis performed by the POC device, which was not specifically controlled for during our study.¹⁸ Finally, we have investigated one POC INR device and conclusions drawn should not be extrapolated to other similar POC devices.

In conclusion, our results support the use of pocINR testing as a rapidly available method for estimating laboratory INR measurements during both the paleohepatic and the anhepatic phases of liver transplantation, but further studies are needed to explore its role in the neohepatic phase. Given the turnaround time in thawing and processing frozen plasma, an elevated pocINR result may prompt the clinician to order blood products expeditiously while awaiting confirmation from laboratory or alternative POC analyses. While the device has utility in aiding transfusion-related decisions after graft anastomosis, results should be verified by laboratory estimation, further POC techniques (e.g., thromboelastography), and clinical assessment of the adequacy of hemostasis.

Conflicts of interest None declared.

References

1. Agarwal A, Sharma N, Vij V. Point-of-care coagulation monitoring during liver transplantation. *Trends in Anaesthesia & Critical Care* 2013; 3: 42-8.
2. Warnaar N, Lisman T, Porte RJ. The two tales of coagulation in liver transplantation. *Curr Opin Organ Transplant* 2008; 13: 298-303.
3. Celenza A, Skinner K. Comparison of emergency department point-of-care international normalised ratio (INR) testing with laboratory-based testing. *Emerg Med J* 2011; 28: 136-40.

4. Maddox JM, Bogo PH, McGregor E, Pippard MJ, Kerr R. Quality assurance for point-of-care testing of oral anticoagulation: a large-scale evaluation of the Hemochron Junior Signature Microcoagulation System. *Int J Lab Hematol* 2009; 31: 142-50.
5. Moore GW, Henley A, Cotton SS, Tugnait S, Rangarajan S. Clinically significant differences between point-of-care analysers and a standard analyser for monitoring the international normalized ratio in oral anticoagulant therapy: a multi-instrument evaluation in a hospital outpatient setting. *Blood Coagul Fibrinolysis* 2007; 18: 287-92.
6. Davenport R, Manson J, De'Ath H, et al. Functional definition and characterization of acute traumatic coagulopathy. *Crit Care Med* 2011; 39: 2652-8.
7. Gauss T, Hamada S, Jurcisin I, et al. Limits of agreement between measures obtained from standard laboratory and the point-of-care device Hemochron Signature Elite(R) during acute haemorrhage. *Br J Anaesth* 2013; 112: 514-20.
8. Mitra B, O'Reilly G, Collecute M, Cameron PA, Phillips L, Davis A. Prospective comparison of point-of-care international normalised ratio measurement versus plasma international normalised ratio for acute traumatic coagulopathy. *Emerg Med Australas* 2012; 24: 363-8.
9. Spielmann N, Mauch JY, Madjdpour C, et al. Comparison of point-of-care testing (POCT): i-STAT® international normalized ratio (INR) vs reference laboratory INR in pediatric patients undergoing major surgery. *Paediatr Anaesth* 2011; 21: 1041-5.
10. McCluskey SA, Karkouti K, Wijeyesundera DN, et al. Derivation of a risk index for the prediction of massive blood transfusion in liver transplantation. *Liver Transpl* 2006; 12: 1584-93.
11. Hanneman SK. Design, analysis, and interpretation of method-comparison studies. *AACN Adv Crit Care* 2008; 19: 223-34.
12. Myles PS, Cui J. Using the Bland-Altman method to measure agreement with repeated measures. *Br J Anaesth* 2007; 99: 309-11.
13. Critchley LA, Critchley JA. A meta-analysis of studies using bias and precision statistics to compare cardiac output measurement techniques. *J Clin Monit Comput* 1999; 15: 85-91.
14. Critchley LA, Lee A, Ho AM. A critical review of the ability of continuous cardiac output monitors to measure trends in cardiac output. *Anesth Analg* 2010; 111: 1180-92.
15. Herbstreit F, Winter EM, Peters J, Hartmann M. Monitoring of haemostasis in liver transplantation: comparison of laboratory based and point of care tests. *Anaesthesia* 2010; 65: 44-9.
16. Green TL, Mansoor A, Newcommon N, Stepheson C, Stewart E, Hill M. Reliability of point-of-care testing of INR in acute stroke. *Can J Neurol Sci* 2008; 35: 348-51.
17. Ryan F, O'Shea S, Byrne S. The reliability of point-of-care prothrombin time testing. A comparison of CoaguChek S® and XS® INR measurements with hospital laboratory monitoring. *Int J Lab Hematol* 2010; 32: e26-33.
18. Hemochron Signature Elite®. Whole Blood Microcoagulation System. Operator's Manual, English. International Technidyne Corporation; 2006. Available from URL: http://www.itcmed.com/uploads/literature/hx1101_0310.pdf (accessed October 2014).
19. Nanduri S, Tayal AH, Hegde GG, Shang J, Venkat A. An analysis of discrepancy between point-of-care and central laboratory international normalized ratio testing in ED patients with cerebrovascular disease. *Am J Emerg Med* 2012; 30: 2025-9.
20. Perry SL, Samsa GP, Ortel TL. Point-of-care testing of the international normalized ratio in patients with antiphospholipid antibodies. *Thromb Haemost* 2005; 94: 1196-202.
21. Solvik UO, Roraas TH, Petersen PH, Stavelin AV, Monsen G, Sandberg S. Effect of coagulation factors on discrepancies in international normalized ratio results between instruments. *Clin Chem Lab Med* 2012; 50: 1611-20.
22. Kettner SC, Gonano C, Seebach F, et al. Endogenous heparin-like substances significantly impair coagulation in patients undergoing orthotopic liver transplantation. *Anesth Analg* 1998; 86: 691-5.