Neuroanesthesia and Intensive Care

Point of care and central laboratory determinations of the aPTT are not interchangeable in surgical intensive care patients

[Les examens visant à déterminer le TCA, réalisés au chevet du malade ou dans un laboratoire central, ne sont pas interchangeables pour les patients des soins intensifs chirurgicaux]

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Purpose: The objective of the study was to compare a bedside whole blood activated partial thromboplastin time (aPTT) performed by a point of care (POC) apparatus (CoaguCheck® Pro) in surgical intensive care (SIC) patients with a conventional aPTT obtained from the central laboratory.

Methods: The prospective concomitant measurements of the two aPTT were performed in 233 samples from 46 consecutive patients admitted after cardiovascular or major abdominal surgery.

Results: Inter-operator, inter-instrument and inter-cartridge variability of the new device measured in three healthy volunteers and in nine patients in stable condition (controls) was low (F test: $P=0.86$). The agreement by Bland and Altman between POC and central laboratory aPTT (-20.2 ± 18.8 sec) was not satisfactory. The agreement between POC and central laboratory aPTT in patients after surgery was worst (-17 ± 33.1 sec). Heparin treatment or timing of blood sampling after intensive care admission (<48 hr *vs* >48 hr) did not influence the agreement. The correlation between POC or central laboratory aPTT and anti-factor Xa activity was poor (r^2 0.077 and 0.181 respectively). The test which correlated the best to heparin doses was anti-factor Xa activity (r^2 0.714).

Conclusion: POC aPTT and central laboratory aPTT showed a poor agreement in SIC patients admitted after surgery, although in healthy volunteers or in control patients, this agreement was better. The best test to monitor heparin treatment in this setting was anti-factor Xa activity.

Objectif : *Comparer le temps de céphaline activé (TCA) du sang total réalisé au chevet du malade (CDM), au moyen d'un CoaguCheck® Pro, avec le TCA traditionnel obtenu d'un laboratoire central, pour des patients aux soins intensifs chirurgicaux (SIC).*

Méthode : *Les mesures prospectives concomitantes des deux TCA ont été faites pour 233 échantillons prélevés auprès de 46 patients successifs admis aux SIC après une opération cardio-vasculaire ou abdominale majeure.*

Résultats : *La variabilité inter-opérateurs, inter-instruments et inter-éprouvettes du nouvel appareil étudié auprès de trois volontaires en bonne santé et neuf patients de condition stable (témoins) a été faible (Test F : $P = 0,86$). Le test de concordance de Bland et Altman entre le TCA (-20,2 ± 18,8 s) réalisé au CDM ou en laboratoire n'était pas satisfaisant. Ce même test réalisé chez des patients après l'opération a été pire (-17 ± 33,1 sec). Le traitement à l'héparine ou la chronologie de l'échantillonnage prélevé après l'arrivée aux soins intensifs (< 48 h vs > 48 h) n'a pas eu d'effet sur la concordance. Il n'existait qu'une très faible corrélation entre le TCA fait au CDM ou en laboratoire et l'activité de l'anti-facteur Xa (r^2 0,077 et 0,181 respectivement). Le test le mieux corrélé aux doses d'héparine a été l'activité de l'anti-facteur Xa (r^2 0,714).*

Conclusion : *Le TCA fait au CDM et le TCA du laboratoire central n'ont affiché qu'une faible concordance chez des patients des SIC admis après l'intervention, même si cette concordance a été meilleure pour des patients témoins et des volontaires en bonne santé. Dans ces circonstances, le meilleur test pour suivre le traitement avec héparine a été l'activité de l'anti-facteur Xa.*

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COAGULATION disorders are observed commonly in surgical intensive care (SIC) patients. Coagulation tests are, therefore, performed frequently, particularly the activated partial thromboplastin time (aPTT) which is used widely because it allows the detection of various coagulation abnormalities as well as the monitoring of heparin therapy.

The time from venipuncture to the availability of aPTT results from the central laboratory can be very long.[1–4] Such delays hinder rapid diagnosis of coagulation disorders and adequate anticoagulation to be achieved rapidly. Rapid knowledge of aPTT results should allow the implementation of measures to decrease bleeding as well as the prevention of thrombotic complications.

A portable bedside point of care instrument (POC: CoaguCheck® Pro, Boehringer Mannheim Diagnostics, USA, Roche Diagnostics, Switzerland), which allows aPTT measurements in three minutes, has been shown to be accurate in both controls, anticoagulated and/or coronary unit patients[1,2,5–7] and therefore may be of interest also in SIC patients. However, there are only few data available on the usefulness and reliability of such a device for these patients.[4,8] The objective of this study was to evaluate prospectively the accuracy of POC in comparison with central laboratory aPTT after cardiovascular or abdominal surgery.

Patients and methods

Patients and data collection

Consecutive patients admitted to the SIC at Geneva University Hospital after cardiovascular or major abdominal surgery were enrolled from July 12 to August 20, 1999. Patients with known previous coagulation disorders were excluded. Patients were tested at six-hour intervals from admission until achievement of normal aPTT values given by the central laboratory. *I V* heparin was then started either for prophylactic or therapeutic use. The aPTT was thereafter determined routinely once daily and four hours after any change of heparin dosing.

To assess the inter-operator, inter-instrument and inter-cartridge variability of aPTT measured by POC, three healthy volunteers and nine SIC stable patients (before SIC discharge, without known bleeding disorder and without coagulation abnormalities) were tested (controls).

The study was approved by the Ethical Committee for Human Research of our institution.

POC and central laboratory aPTT and anti-factor Xa activity

The aPTT was determined both in the central laboratory (conventional method) and in the SIC (POC). Blood was drawn into a syringe by direct venipuncture whenever possible, or through an arterial catheter from which 10 mL (ten times the dead space) of blood[4] were withdrawn prior to collection of the sample in order to minimize its contamination with heparin from the continuous irrigation systems attached to the invasive catheter. A drop of whole blood was deposited on the prewarmed aPTT cartridge of the POC, and the remainder dispensed into the tube for central laboratory assessment. The maximum delay between blood sampling and central laboratory measurement was 60 min.

For the aPTT determined in the central laboratory, plasma (citrated blood, 0.129 $mol \cdot L^{-1}$ sodium citrate) was obtained by centrifugation at 3500 x g for ten minutes at 15–20°C. Actin (Dade Behring) was used as the source of phospholipid and activator (ellagic acid). The tests were performed with automated coagulometers, either a Behring Coagulation System or a Behring Coagulation Timer (all from Dade Behring, Marburg, Germany). Maximal measuring time was set at 200 sec, the reference range being 25 to 31 sec.

Heparin concentrations were evaluated with an anti-factor Xa (anti-FXa) chromogenic assay (Berichrom Heparin, Dade Behring) and the Behring Coagulation System. Since bovine antithrombin is also present in the reagent, the test is independent of its actual concentration in the sample.[9] The target values depends on the clinical situation (therapeutic ranges from 0.3 to 0.6 $U \cdot mL^{-1}$).

The POC provided by CoaguCheck® Pro is a battery-powered, portable laser photometer using a phospholipid (soybean phosphatide) as platelet substitute and a bovine brain sulfatide as activator of intrinsic coagulation. 45 μL samples of capillary, arterial or venous whole blood can be used. Instructions for use were explained to the nursing team during 20 min teaching sessions, three times per week, for four weeks. The monitors were checked every two days (20 measurements) with two level control cartridges. Each two weeks, a lyophilized whole blood internal quality control was conducted. Reference interval was established previously by the manufacturer (range 20.2 to 40.8 sec). Three portable devices were utilized. Inter-operator, inter-instrument and inter-cartridge variability of POC aPTT was determined by simultaneous analysis of the same blood sample drawn from 12 control patients by three different nurses.

Data were analyzed according to the administration of heparin, aprotinin, aspirin and clopidogrel before SIC admission.

Statistical analysis

Statistical analysis was performed on a Macintosh computer utilizing Statview II software (Abacus Concepts, Berkeley, California, USA). Results were analyzed either by Bland and Altman[10] for comparison of similar assays and by linear regression analysis for different assays. To be interchangeable, we determined *a priori* an upper limit of ten seconds as an acceptable difference between the two methods, as it would not modify clinical management. Inter-operator, inter-instrument and inter-cartridge variability of POC aPTT were assesed by F test. We planned to analyze >200 samples to demonstrate in different subgroups of 25 samples a r >0.4 with $P < 0.05$.

For calculation purposes, when a sample was not clottable, an arbitrary 200 sec clotting time was assigned (three samples with POC aPTT and two samples with central laboratory aPTT and two with both tests).

Results

SIC patients

Forty-six patients were included in the study. Table I shows the patients' characteristics on admission. Two hundred thirty-three aPTT measurements were realized, 181 from cardiovascular and 52 from abdominal surgery patients. For each point, the difference between the clotting times obtained with the two assays was plotted as a function of their mean. Only clottable samples are represented. As shown in Figure 1, agreement between central laboratory aPTT and POC aPTT was poor (-17 ± 33.1 sec). There was an important dispersion of values and a trend towards longer clotting times with POC. When the patients were divided according to the type of surgery, the agreement was slightly better in abdominal (-23.3 ± 25.5 sec) than in cardiovascular surgery patients (-15.2 ± 35 sec). The mean difference between the two methods was lower in samples collected in the initial 48 hr (-11.5 ± 33 sec) as compared to samples collected after 48 hr (-27.5 ± 31 sec). Heparin did not influence the agreement (-20.8 ± 27 sec).

POC as well as central laboratory aPTT values correlated poorly with heparin dosage (r^2 0.035 and r^2 0.061 respectively) and anti-FXa (r^2 0.077 and 0.181 respectively). The best correlation with heparin dosage was obtained with anti-FXa activity measurements (r^2 0.714; Table II).

Aprotinin administration (n=14) during extracorporeal circulation or protamine administration (n=26) before SIC admission did not influence significantly the degree of agreement between central laboratory and POC aPTT (data not shown). Antiplatelet agent (aspirin and clopidogrel), renal insufficiency/failure, hepatic alterations, anemia, thrombocytopenia and temperature alterations before or during SIC did not alter the agreement between central laboratory and POC aPTT (data not shown).

In all the subgroups, the 95% of differences between the two methods fell outside the *a priori* assigned ± 10 sec difference required to accept the interchangeability of the methods.

Controls: Healthy volunteers and stable SIC patients

POC aPTT measurements performed by three nurses (three devices) on the same samples showed good correlation between each other (F test: P=0.86). In these samples, the agreement between mean POC aPTT and central laboratory aPTT values was better (-20.2 ± 18.8 sec) than in control SIC patients (Figure 2).

TABLE I Patients characteristics at SIC admission (n=46)

Age	years (mean ± SD)	61 ± 14
Sex	males/females (n/n)	33/13
Body weight	kg (mean ± SD)	76 ± 18
Diagnosis		*n*
	Cardiovascular surgery	30
	Cardiac surgery	26
	Aortic surgery	4
	Abdominal surgery	16
	Hepatic surgery	2
	Intestinal surgery	10
	Pancreatic surgery	1
	Biliar surgery	3
Therapy before SIC admission		*n*
	Heparin	38
	Protamine	26
	Aprotinin	14
	Aspirin	6
	Clopidogrel	1

TABLE II Correlation between CoaguCheck® Pro aPTT, central laboratory aPTT, anti-FXa assay and heparin dosage

Comparison	*Number of samples*	*Correlation coefficient r^2*
CoaguCheck® aPTT/ heparin dosage	136	0.035
CoaguCheck® aPTT/ anti-FXa assay	71	0.077
Central laboratory aPTT/ heparin dosage	136	0.061
Central laboratory aPTT/ anti-FXa assay	71	0.181
Anti-FXa assay/ heparin dosage	52	0.714

aPTT=activated partial thromboplastin time; anti-FXa=anti-factor Xa.

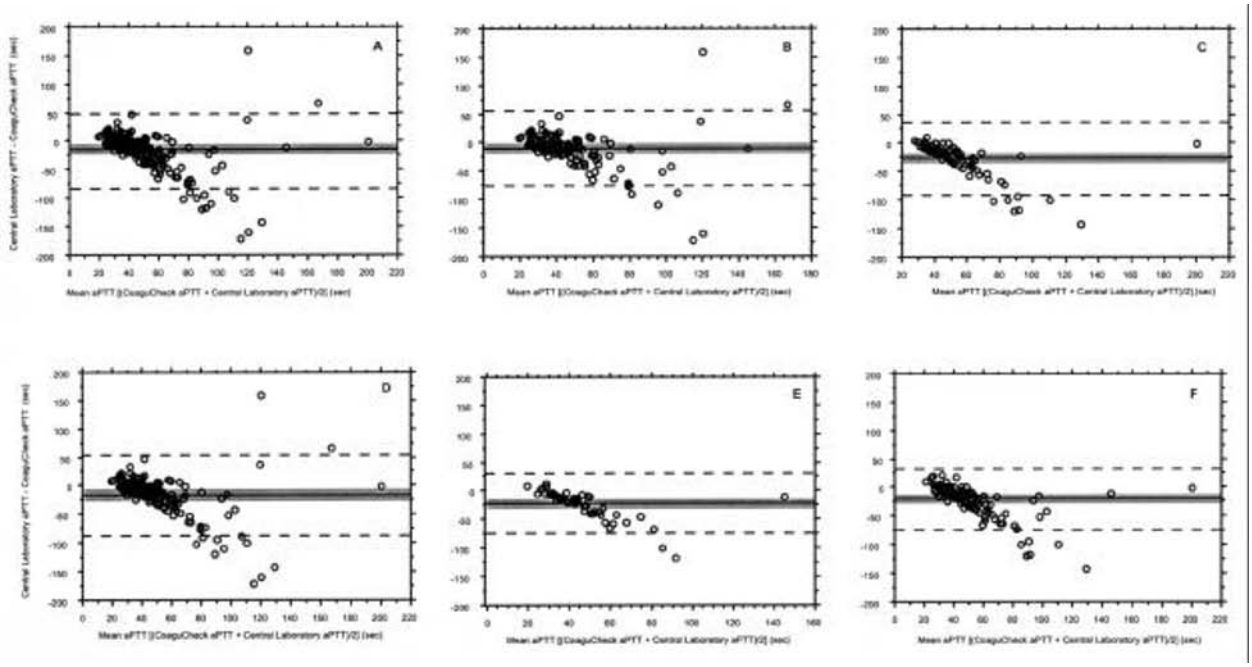

FIGURE 1 Agreement between activated partial thromboplastin time measured by CoaguCheck® Pro point of care and by central laboratory in different situations (A-F). The bias represents the systematic error between the two assays (bold line), the mean difference ± 2 standard deviations represents the limit of agreement or the 95% confidence interval (dotted line). The confidence interval of the difference between the two methods falls in all subgroups outside the *a priori* required upper limit of ± 10 sec (grey area) to accept the interchangeability of methods. Samples that were not clottable with one or both assays were omitted.
A: Samples drawn from all patients; B: Samples drawn from cardiovascular patients; C: Samples drawn from abdominal surgery patients; D: Samples obtained during initial 48 hr surgical intensive care unit (SICU) stay; E: Samples obtained 48 hr after SICU admission; F: Samples drawn from patients on heparin therapy.

The correlation between central laboratory aPTT and heparin doses or anti-FXa activity was good (r^2 0.932 and r^2 0.841 respectively) and the correlation between mean POC aPTT values and heparin doses or anti-FXa activity was satisfactory (r^2 0.700 and r^2 0.484).

Discussion

Our study in patients just admitted in SIC after surgery shows that the agreement between aPTT values obtained with POC and those from the central laboratory is poor, in contrast to the results obtained in controls. No acceptable agreement was found when considering either all patients, subgroups of patients or controls. Indeed, the data presented in Figure 1 indicate that the two assays give discordant results. POC aPTT tend to be longer than central laboratory aPTT and this difference tends to increase with prolonged aPTT. Heparin and all other treatments tested or the time after SICU admission did not appear to be associated with the poor agreement observed. Analysis of subgroups of patients and of samples drawn in different clinical conditions, or under different therapeutic regimens, could not identify a major factor influencing the agreement or the correlation.

The discrepancy between central laboratory and POC aPTT values may be due to the variable reductions in multiple coagulation factors in patients at their arrival to SIC. It can hardly be due to mishandling of the new device since variability of measurements made by three well-trained nurses was low. The agreement between POC aPTT and central laboratory aPTT in controls were found to be better, confirming previous data.[1–7,11–14]

Our results are partly in line with other studies which have evaluated POC in cardiac surgery patients. Reich *et al.*[8] studied 141 patients and considered an accuracy of ± 10% and a precision of ± 25% as clinically acceptable. The mean error for the aPTT values was plus seven seconds and the 95% confidence interval for the bias was -21 to + 35 sec, which were considered

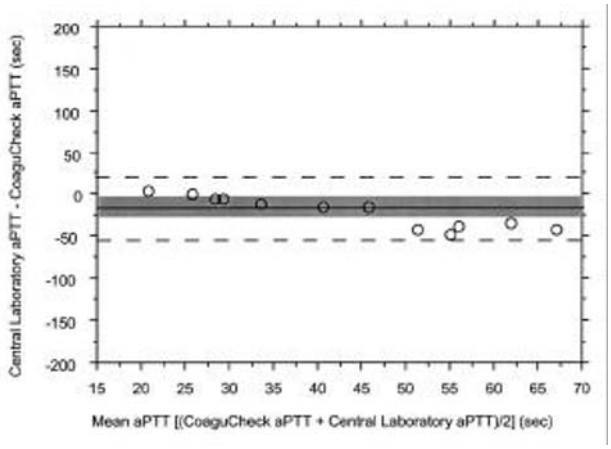

FIGURE 2 Agreement between point of care and central laboratory activated partial thromboplastin time in healthy volunteers and control patients. The bias represents the systematic error between the two assays (bold line), the mean difference ± 2 standard deviations represents the limit of agreement or the 95% confidence interval (dotted line). The confidence interval of the difference between the two methods falls outside the *a priori* required upper limit of ± 10 sec (grey area) to accept the interchangeability of methods.

unsatisfactory for patient management. Nuttall *et al.*,[15] using also a Ciba Corning 512 Coagulation Monitor (the previous model of CoaguCheck® Pro), enrolled 100 patients following cardiopulmonary bypass surgery and found a correlation coefficient (r) of 0.95 between the portable device and central laboratory measurements in arterial samples drawn ten minutes after heparin neutralization. This result is far better than the one found in our study for samples without heparin (r 0.354). However, in a subsequent analysis of 148 patients, the same authors[16] reported a positive and negative predictive value for bleeding tendency after cardiopulmonary bypass with bedside aPTT devices of only 33% and 89% respectively. Boldt *et al.*[4] studied 80 patients and found an agreement of -2.8 ± 16.5 sec with POC. The time of sampling and the influence of heparin were not mentioned. Careful examination of their data indicates that the scatter of values is about three fold less than ours. Nevertheless, the 95% confidence interval reported implies a total possible difference up to 32 sec for any single measurement, which seems considerable.

In the study by Despotis *et al.*,[17] the bias analysis of the aPTT performed by the central laboratory or the bedside device revealed an agreement of +10 ± 28.8 sec. Thus, all studies have shown an agreement with a confidence interval of the difference between the two methods superior to the *a priori* determined acceptable upper limit of ten seconds.

It is well known that using the same plasma, various commercial aPTT reagents give different results.[18] This is particularly true for aPTT testing in heparinized patients where deviations up to 200% have been reported.[19] Werner *et al.*[20] studied the effect of analytical uncertainty of conventional and bedside assays of aPTT on clinical decisions in heparin therapy. Despite an overall agreement of about 70%, the bedside coagulation instrument correctly classified only seven (39%) of 18 specimens with subtherapeutic concentrations of heparin. In summary, our results are not unexpected, particularly given the non standardized nature of the aPTT assay, the numerous variables that can influence aPTT immediately after surgery and the different responses of both methods to factor deficiencies and heparin.[17]

Monitoring heparin anticoagulation in patients who have undergone surgery associated with extracorporeal circulation represents a challenge since global tests are affected by heparin administration, possible excess protamine, acquired factor(s) deficiency, disseminated intravascular coagulation, isolated primary hyperfibrinolysis as well as use of volume expanders. The relationship between the degree of anticoagulation and the extent of clotting time prolongation of global tests like the aPTT is not easy to establish, because of a wide variability in confounding factors, in individual response and also in differences in aPTT reagents and devices. Chromogenic anti-factor assays for determination of heparin concentration allow to estimate the actual contribution of heparin to the degree of anticoagulation induced by both the drug and the hemostatic abnormalities. Therefore, dose adjustments of heparin anticoagulation are difficult to achieve with the aPTT only, especially in this type of patients. This may explain the better correlation observed between heparin dosage and anti-FXa activity than between heparin dosage and either POC aPTT or central laboratory aPTT, which is due probably to the impact of low AT III and coagulation factor levels not affecting anti-FXa activity.

In conclusion, the agreement between POC and central laboratory aPTT was poor in SIC patients after surgery but better in controls. These two tests give potentially different information and only a prospective trial comparing their usefulness for predicting clinical events could allow to establish their respective utility in postoperative SIC patients.

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