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Evaluation of the GEM®PCL Plus point-of-care device for neonatal coagulation assessment: An observational study on cord blood

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ABSTRACT

Introduction: Point of care devices (POCT) are used for coagulation evaluation in adults. Reduced blood volumes and the direct use of whole blood allow studies when venous puncture is difficult, such as in newborns. Elimination of sample transport is attractive for use in emergencies and intensive care.
Objective: To prospectively compare neonatal coagulation parameters measured by the GEM®PCL POCT versus a central laboratory.
Materials and Methods: Prothrombin Time (PT) and activated Partial Thromboplastin Time (aPTT) were performed on whole cord blood (POCT) and plasma (central laboratory) collected from consecutive newborns at Geneva University Hospitals. Agreement was assessed with a Bland & Altman plot and intra-class correlation coefficient (ICC) in 213 newborns cord blood; intra-assay variability (repeatability) was assessed using ICC and coefficient of variation (CV).
Results: 189 samples were available for the agreement analysis, 24 were excluded for technical problems. The 95% limits of agreements in the Bland & Altman plot ranged from -5.6 to 11.6 and from -39.6 to 11.6 seconds for the PT and aPTT, respectively. The ICC between the two methods was 0.28 (CI 95% 0.06 to 0.47) for PT and 0.20 (CI 95% -0.06 to 0.42) for aPTT. Repeatability (ICC) on the 43 eligible samples was 0.46 (CI 95% 0.19 to 0.67) for PT and 0.52 (CI 95% 0.26 to 0.71) for aPTT. The CV was 10.6% and 12% for PT and aPTT, respectively.
Conclusions: In newborn cord blood, PT and aPTT measurements with the GEM®PCL POCT had poor agreement with the central laboratory and poor repeatability.

Introduction

Bleeding disorders and haemorrhages are frequent in neonates, but insight into their causes has been hindered by the limited clinical use of coagulation assessments, in part because baseline coagulation profiles, including Prothrombin Time (PT), activated Partial Thromboplastin Time (aPTT) and fibrinogen assays require sample sizes of 0.9 mL to 2 mL of citrated blood. In a 500 g neonate, a single sample could thus remove 5% of total blood volume. An elevated haematocrit—a common feature in neonates—is another factor that may result in pre-analytical errors [1] and thus limit accurate determinations of coagulation profiles.

Evidence supports the use of point-of-care testing (POCT) for effective coagulation evaluation in adults [2–5], especially to monitor vitamin K antagonists [6,7]. Anticoagulant therapy can be safely and reliably monitored in children using POC devices [8–12], but very little data exist for the neonatal population [8,13]. In theory, there would be several practical advantages to the use of POCT in the neonatal population; these include using up to 10 times less blood by volume and the direct use of whole blood, possibly eliminating the need for a venous puncture. Simple handling and the elimination of sample transport minimize pre-analytical errors. A particular advantage of POCT is the immediate availability of results in the neonatal intensive care unit, allowing prompt clinical decisions [14,15].

This study's main objective was to evaluate the agreement and repeatability of PT and aPTT for such POCT (GEM®PCL Plus) on whole blood from newborns, compared to conventional assays on plasma performed in the central laboratory.

Material and Methods

Design

For this prospective observational study, which ran from June to December 2012, umbilical venous blood samples were obtained from

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consecutively born neonates immediately at birth. Except for refused parental informed consent, no exclusion criteria were applied. The University Hospitals of Geneva Central Ethics Committee approved the study protocol (CER 10-176).

Sampling and Measurements

The POCT coagulometer (GEM®PCL Plus, Instrumentation Laboratory, Bedford, USA) used a 50-μL (one drop) whole blood sample for each test; this is inserted into the device on a test cartridge. The clotting process is initiated by thromboplastin (thromboplastin ISI:1) for PT and kaolin for aPTT, and the time to clot formation is recorded. The mechanical-endpoint clotting is detected optically. The coagulometer was calibrated with lot-specific cartridge code chips. Quality control experiment was performed with an electronic control of temperature and with electronic PT and aPTT cartridges once per week throughout the study period. A liquid control sample for PT and one for aPTT were also runned once each two weeks.

One mL of blood was collected from the umbilical vein immediately after placental delivery. Blood collection was done by a plastic syringe and the needle was systematically removed before sub-sampling. 100 μL of whole blood were used to measure PT and aPTT using POCT, and 900 μL of blood were collected into a 0.109 M citrated tubes (BD Vacutainer™, Becton Dickinson, Meylan, France), so the same tests could be performed by the central laboratory within 4 hours. A BCS XP haemostasis analyser (Siemens, Marburg, Germany) was used with Innovin and Pathromtin SL reagents (Siemens) for PT and aPTT, respectively.

The intra-assay variability (repeatability) of the POCT device was evaluated using 4 consecutive 100-μL samples of whole blood from an additional 48 consecutive newborns. These tests were performed using simultaneously two coagulometers.

Data Analysis

PT and aPTT were expressed as means and standard deviations for both POCT and central laboratory results. Agreement (reproducibility) between measurements was assessed using Bland-Altman plots [16,17] and intra-class correlation coefficients (ICC). In a secondary analysis we dichotomized each technique measures according to their respective upper quartile (75th percentile) and assessed agreement between the two methods using a kappa analysis [18]. Repeatability of POCT was assessed using ICC and coefficient of variation (CV) [19]. Because of coagulation problem (i.e. blood clot before measurement), repeatability analysis was performed on the first two measures rather than on the four measures as initially planned. Finally, intra-class correlation coefficients were determined using one-way random effect model for intra-rater (repeatability) analysis and two-way mixed model, absolute agreement definition for inter-rater (reproducibility) analysis.

Study Sample Size

The sample size necessary to determine an ICC of 0.8 with a precision (width of the two-sided 95% confidence interval) of 0.1, was 200 [20]. For the repeatability analysis, a sample size of 40 with 4 consecutive measurements was sufficient to estimate an ICC of at least 0.8 with a precision lower than 0.2. In order to anticipate a possible coagulation problem in 15% of patients, 48 patients were included [20].

Results

Two hundred and sixty-one consecutive newborns were enrolled in this study: 213 for the agreement analysis and 48 for the repeatability analysis. Of the 213, 24 samples had to be excluded because of technical errors: 9 due to inappropriate filling of the cartridge and/or an error message on the GEM®PCL Plus; 8 due to inappropriate filling of the citrated tube for the central laboratory; and 7 due to both. Repeatability analysis was performed on the first two measurements of 43 of the 48 samples included; 5 had to be rejected due to a coagulated sample in one or more determinations (Fig. 1). The haematocrit of these samples ranged from 29.2% to 55.8%.

Of the 189 neonates analysed, 47% were female and 53% male, the mean gestational age was 39 weeks (±1.9 weeks) and mean weight was 3,280 g (±570 g).

The comparative coagulation results determined by POCT and the central laboratory are summarized in Table 1. As indicated in Table 2, the ICC between the two methods was 0.28 (95% CI, 0.06 to 0.47) for PT and 0.20 (95% CI, -0.06 to 0.42) for aPTT. The Bland-Altman plot showed a mean difference between POCT and the central laboratory of 3.0 and -14.0 seconds for PT and aPTT, respectively; the 95% limits of agreements ranged from -5.6 to 11.6 seconds for PT and from -39.6 to 11.6 seconds for aPTT (Fig. 2A and B). The kappa analysis of each method's upper quartile was 0.449 ($p < 0.001$) for PT and 0.282 ($p < 0.001$) for aPTT.

Assessment of the repeatability of GEM®PCL Plus POCT yielded an ICC of 0.46 (95% CI, 0.20 to 0.67) for PT and 0.52 (95% CI, 0.27 to 0.71)

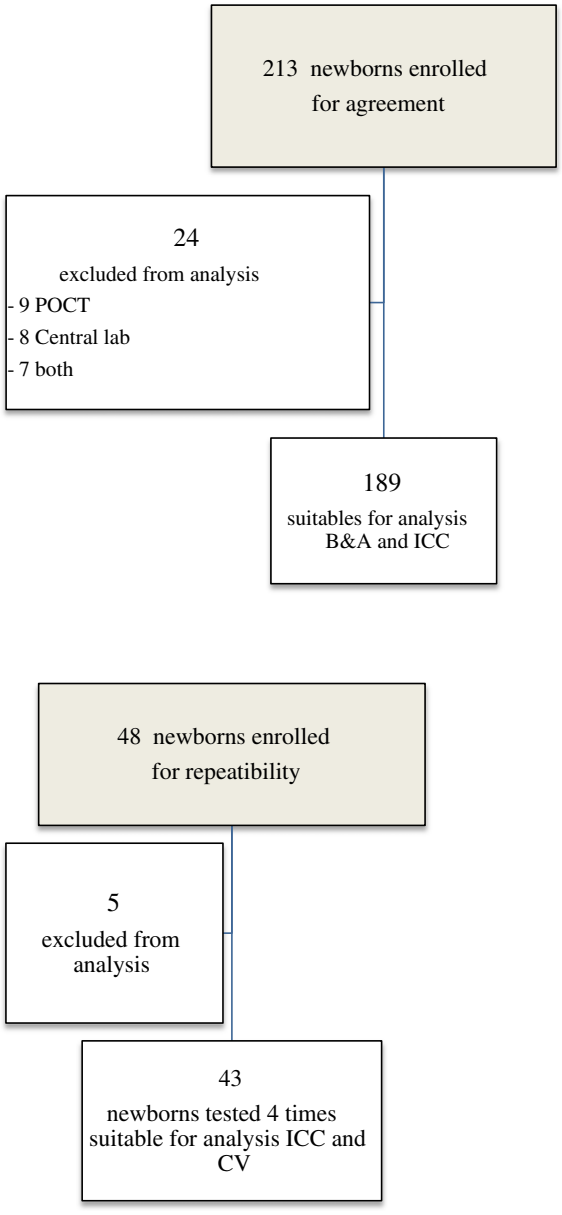

Fig. 1. Flow chart of the study (Agreement and Repeatability studies).