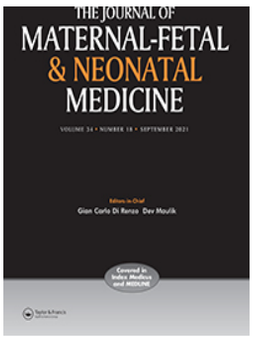

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ORIGINAL ARTICLE

Impact of blood sampling technique on reproducibility of viscoelastic coagulation monitor (VCM™) system test results in the neonate

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ABSTRACT

Purpose: To evaluate the reproducibility of the results of the viscoelastic coagulation test (VCT) performed with a new viscoelastic coagulation monitor (VCM™ – Entegrion) on native blood obtained by heel prick blood sampling with two different techniques compared to the standard blood collection in the newborn.

Methods: Three blood samples were tested with the VCM analyzer in each of the 67 study subjects admitted to our level 3 neonatal intensive care unit. Standard blood collection (S) was performed by direct puncture of a peripheral vessel or by drawing of blood in a syringe connected to an arterial or venous catheter. Then, two more blood samples were drawn through a single heel prick. The first heel prick blood sample (HP1) was collected in the sample well through the attached metal capillary while the second (HP2) was poured directly into the sample well. Blood samples were automatically drawn into their pre-warmed cartridges and inserted into the VCM analyzers set up for analyses, which ran for one hour. VCT blood variables included clotting time (CT), clot formation time (CFT), angle alpha (α), amplitude at 10 and 20 min (A10 and A20), maximum clot firmness (MCF), and lysis indexes at 30 and 45 min (LY30 – LY45). Agreement was quantified by calculating the mean difference and SD between measurements of VCT blood variables from S, HP1 and HP2 blood samples. The 95% limits of agreement were calculated by the Bland & Altman method, using the upper or lower limit of agreement to interpret the variability of the measurements. The Kendall's τ correlation coefficient evaluated the interdependence between SD and intra-measurement mean.

Results: S blood samples were easily obtained in all the study subjects, while mild difficulties were recorded in 3/67 infants (4.5%) with the HP1 blood sampling and in 5/67 infants (7%) with the HP2 blood sampling. Pairwise comparison of test results performed on blood samples drawn with HP1 and HP2 techniques showed moderate agreement for CT and α-angle, strong agreement for CFT, LY30 and LY45 and almost perfect agreement for A10, A20 and MCF. In pairwise comparison of VCM analyses performed on blood samples drawn with S technique vs HP1 and HP2 techniques, Kendall's τ correlation coefficient was significant for CT (S vs HP1 and HP1 vs HP2), CFT (S vs HP1 and S vs HP2), α-angle (S vs HP1) and MCF (S vs HP1). This suggests that the measurement error depends on the extent of the measurement. The overall ICC for blood sampling techniques ranged from 0.289 to 0.879 with best agreement observed for CFT (strong) and for A10, A20 and MCF (almost perfect). The LY30 index was the least repeatable measurement (poor agreement). The VCM analysis performed on the blood sample drawn with the HP1 technique showed the best repeatability compared with that performed with the S blood-sampling technique.

Conclusion. VCT test results performed with the VCM analyzer on native blood drawn by heel prick in neonates are comparable to those obtained from standard blood samples. This could allow for a widespread, real-time assessment of the overall bedside haemostasis of these small patients.

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Thromboelastography; heel prick blood sampling; viscoelastic coagulation test

Introduction

The viscoelastic coagulation test (VCT) promises a rapid assessment of the full hemostatic potential in the newborn [1]. The VCM™ system (Entegrion, Durham, NC, USA) is a new viscoelastic coagulation monitoring system with interesting features for a neonatologist, such as the ability to perform an automated test with a small amount of fresh whole blood

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without the need to manipulate samples and free of chemical accelerants avoiding modifications to the native properties of the patient sample [2].

Blood sampling for VCM test is normally performed by the direct puncture of a peripheral vein or artery or drawing blood from an arterial or venous catheter. These techniques can be challenging and sometimes even dangerous in hospitalized sick infants [3–5], especially if extremely premature, where heel prick blood sampling remains the preferred method for laboratory tests that require small amounts of blood [6,7]. The ability to use a small amount of native blood with the VCM analyzer makes it theoretically possible to use heel prick blood sampling, which could facilitate bedside assessment of the overall hemostatic function of sick children.

Our aim was evaluating the feasibility of using heel prick blood sampling with VCM analyzer and the reproducibility of the test results compared to standard blood sampling.

Materials and methods

We performed a prospective observational study on a series of infants admitted to our NICU to evaluate the reproducibility of the VCT test results performed with the VCM analyzer on fresh whole blood samples collected simultaneously with different sampling techniques (standard vs heel prick blood draw) and run in parallel. Blood samples collected for the study were in addition to scheduled blood draws and test results never guided treatment.

We conducted this study under the amended Declaration of Helsinki on the ethical conduct of research involving human subjects.

Patient population

We chose to estimate the intra-class correlation coefficient (ICC) to calculate the sample size of the study subjects, which is usually determined based on the expected width of a confidence interval (CI) [8]. A sample size of 67 patients yielded to a 95% confidence interval equal to the sample CI plus or minus 0.1 when the CI estimate is 0.7. These study subjects were consecutively recruited from September 2020 to February 2021.

Blood sampling techniques

Standard blood sampling (S) for VCM analysis was performed by the direct puncture of a peripheral vessel (arterial or venous) or by drawing blood into a 1 ml syringe connected to the catheter hub port of an arterial or venous catheter. In these cases, adequate initial blood volume was discarded and heparin-contaminated lines avoided. After blood collection, 0.3 ml of whole fresh blood were poured into the sample well of a pre-warmed VCM cartridge. Once the space between the glass disks of the cartridge was filled with blood, the sample addition cup was removed and discarded, and the cartridge was placed in the VCM analyzer set up for patient testing.

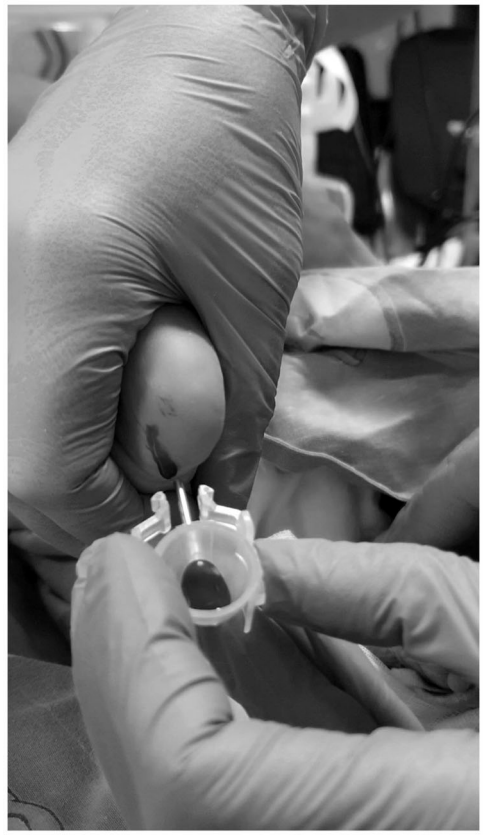

Figure 1. Heel prick blood sample (HP1) collected by flowing the blood from the heel into the sample well through the attached metal capillary.

Subsequently, two further samples with similar blood amount were drawn through a single heel prick performed with an automated device (Tenderfoot Newborn Lancet) after adequate heel pre-warming. The first heel prick blood sample (HP1) was collected by flowing the blood from the heel into the sample well through the attached metal capillary as shown in Figure 1. Next, a second blood sample (HP2) was collected by pouring the blood directly into the sample well with a slight heel squeezing as shown in Figure 2. When adequately filled, the sample addition caps were re-attached to their respective pre-warmed

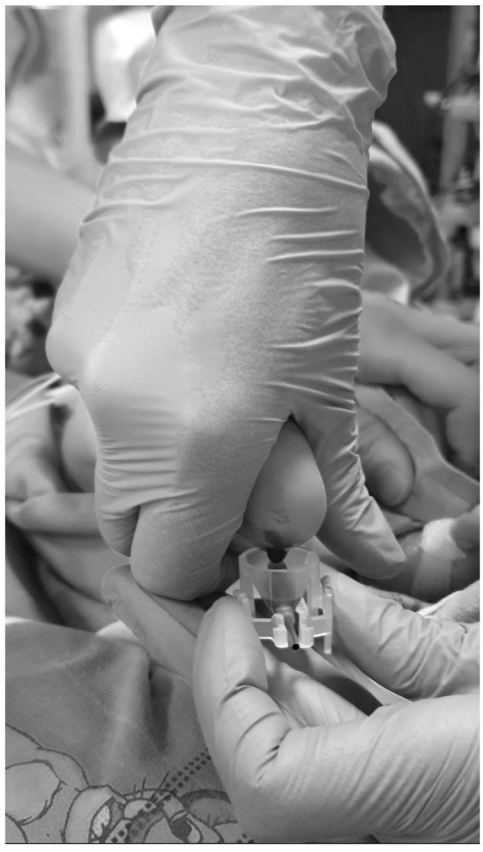

Figure 2. Heel prick blood sample (HP2) collected by pouring the blood directly into the sample well with a slight heel squeezing.

cartridges. Again, once the space between the glass disks of the cartridges was filled with blood, the sample addition cups were removed and discarded and the cartridges were placed in their respective VCM analyzers set up for patient testing.

VCM analysis

A detailed explanation of how the VCM analyzer works and how to test with the VCM system is beyond the scope of this paper and can be found elsewhere [2].

VCT blood variables measured included clotting time (CT) and clot formation time (CFT), expressed in minutes; alpha-(α) angle, expressed in degrees; amplitude at 10 and 20 min (A10 and A20) and maximum firmness of the clot (MCF), expressed in VCM units; lysis indexes at 30 and 45 min (LY30 and LY45), expressed as percentage of the MCF.

All VCM tests started automatically from blood collection within four minutes once the VCM analyzer door was closed and ran for one hour. A single operator (MR) supervised all blood samplings and VCM test runs. Quality control checks were run on each instrument used for this study according to recommendations in the VCM operator manual. No tests were run on instruments that failed quality control check.

Statistical analysis

A descriptive analysis was performed, determining the mean and standard deviation (SD) of each variable. Reproducibility was assessed by means of agreement and reliability measures. Agreement parameters estimate the measurement variability in repeated measurements. Reliability parameters assess whether study objects can be distinguished from each other, despite measurement variability that is related to inter-patient variability.

Agreement

Agreement was quantified by calculating the mean difference and SD between the standard blood sample (S) the heel-prick blood sample drawn by the metal capillary (HP1) and the heel-prick blood sample squeezed into the sample well (HP2). The 95% limits of agreement were calculated by the Bland & Altman method for VCT blood variables from different blood sampling techniques, with the upper or lower limit of agreement being used to interpret measurement variability [9]. Kendall's τ correlation coefficient assessed the interdependence of intra-measure SD and mean.

Reliability

The intra-class correlation coefficient (ICC) indicates the inter-patient variance to total variance ratio (11). It was derived from a random-effects one-way analysis of variance. ICC values are as follow: 0–0.2 indicates poor agreement: 0.3–0.4 indicates fair agreement; 0.5–0.6 indicates moderate agreement; 0.7–0.8 indicates strong agreement; and $>$ 0.8 indicates almost perfect agreement [10].

Statistical analyses were performed using IBM-SPSS® version 26.0 (IBM Corp., Armonk, NY, USA, 2019), and StatsDirect version 2.7.2 (StatsDirect Ltd, Altrincham, Cheshire, UK, 2008).

Results

Of the 67 enrolled infants, 31 (46.3%) were uncomplicated preterm, 13 (19.4%) surgical, 7 (10.4%) had respiratory distress syndrome, 7 (10.4%) were asphyxiated infants treated with therapeutic hypothermia, 4

Table 1. VCT blood variables measured by VCM analyzer and their differences due to different blood sampling techniques.

	Mean ± SD			Differences in mean ± SD		
	S	HP1	HP2	S-HP1	S-HP2	HP1-HP2
CT (min.)	5.9 ± 1.7	3.9 ± 2	3.1 ± 1.5	2 ± 1.9	2.8 ± 1.8	0.8 ± 1.6
CFT (min.)	2.7 ± 1.3	3.1 ± 1.9	3.1 ± 2.3	−0.4 ± 1	−0.4 ± 1.7	0 ± 1.5
α-Angle (°)	57.8 ± 8.2	53 ± 10	55.2 ± 13.1	4.8 ± 6.4	2.6 ± 11	−2.1 ± 10.4
A10 (VCM U)	26.9 ± 8	27.3 ± 8.9	26.9 ± 10.2	−0.4 ± 3.9	0 ± 5.1	0.4 ± 4.7
A20 (VCM U)	32.8 ± 8.6	34.1 ± 9.7	33.1 ± 10.6	−1.2 ± 4.2	−0.3 ± 5.3	1 ± 4.9
MCF (VCM U)	34.3 ± 8.6	36.5 ± 9.7	35.4 ± 10.5	−2.2 ± 4.4	−1.1 ± 4.9	1.1 ± 4.9
LI30′ (%)	99.7 ± 0.7	99.9 ± 0.4	99.9 ± 0.5	−0.2 ± 0.8	−0.2 ± 0.8	0 ± 0.3
LI45′ (%)	96.6 ± 3	97.6 ± 2.7	98 ± 2.3	−1 ± 2.7	−1.3 ± 2.7	−0.4 ± 1.6

A10: Amplitude at 10 min; A20 amplitude at 20 min; CFT: clot formation time; CI: confidence interval; CT: clotting time; HP1: heel prick blood sample by metal capillary; HP2: heel prick blood sample squeezed; ICC: intra-class correlation coefficient; MCF: maximum clot firmness; LY30: lysis index at 30 min; LY45:lysis index at 45 min; S: standard blood sample; U: units; VCM: viscoelastic coagulation monitor; VCT: viscoelastic coagulation test. Data are expressed as mean ± DS.

(6%) infected, 3 (4.5%) had haematological conditions and 2 (3%) congenital heart disease.

S blood samples for VCM analysis were easily obtained in all the study subjects as follows: from a peripherally inserted central catheter in 29 infants (43.3%), from an umbilical venous catheter in 17 infants (25.4%), from direct puncture of a peripheral artery in 17 infants (25.4%) and from a venipuncture in 4 infants (6%). Drawing blood from the heel prick was also easy, with mild difficulties recorded in only 3/67 infants (4.5%) with the HP1 and in 5/67 infants (7%) with the HP2 blood sampling technique. These difficulties were mainly represented by obstruction of the metal capillary during blood collection and by inadequate heel bleeding due to peripheral vasoconstriction. The mean ± SD values of the VCT blood variables measured by VCM analyzer and their differences due to different blood sampling techniques are shown in Table 1.

Pairwise comparison of VCM analyses performed on blood samples drawn with HP1 and HP2 techniques showed moderate agreement for CT and α-angle, strong agreement for CFT, LY30 and LY45 and almost perfect agreement for A10, A20 and MCF (Table 2). In pairwise comparison of VCM analyses performed on blood samples drawn with S technique vs HP1 and HP2 techniques, Kendall's τ correlation coefficient was significant for CT (S vs HP1 and HP1 vs HP2), CFT (S vs HP1 and S vs HP2), α-angle (S vs HP1) and MCF (S vs HP1). This suggests that the measurement error depends on the extent of the measurement. In particular, the error for CT and α-angle measurements increases for the shorter time/lower degree values between S and HP1 blood-sampling techniques, while the error for CT increases for the longer time values between HP1 and HP2 blood-sampling techniques (Table 2).

The overall ICC for blood sampling techniques ranged from 0.289 to 0.879 with best agreement observed for CFT (strong) and for A10, A20 and MCF (almost perfect) (Table 2). The LY30 index was found to be the least repeatable measurement (poor agreement) due to the scarcity of possible values that makes correct reclassification with ICC difficult. Instead, LY 45 index values allowed a better ICC reclassification and showed moderate agreement between different blood sampling techniques.

The VCM analysis performed on the blood sample drawn with the HP1 technique showed the best repeatability compared with that performed with the S blood-sampling technique. An overview and summary evaluation of the results are provided in Table 3.

Discussion

The interpretation of neonatal coagulation test results is not an exact science. Developmental haemostasis, pre-analytical and analytical issues and the lack of age, analyzer and reagents appropriate reference ranges for coagulation screening together with the technical challenges associated with blood drawing in neonates have an important impact on both the diagnosis and management of the hemostatic imbalance in infants and may lead to inappropriate transfusions of blood products [11–13]. Newer VCT assays assessing the stages of hemostasis including clot initiation, propagation, and fibrinolysis in the whole blood by viscoelastic methods allow for a global measurement of the hemostatic system [1,14]. However, the most widely used systems involve the use of citrated blood samples [1], require several blood sample manipulations and adherence to standardized blood sample processing, which potentially increase the risks of pre and analytical errors in the busy NICU's environment, as the neonatologist is not a lab technician. Another important limitation of these systems is that they do not provide for using capillary blood sampling, which instead represents a consolidated practice in infancy.

Table 2. Comparison and agreement of test results of the VCM analyses according to different blood samples techniques.

	Lower and upper limits of agreement			Kendall's t			ICC				
	S-HP1	S-HP2	HP1-HP2	S-HP1	S-HP2	HP1-HP2	S-HP1	S-HP2	HP1-HP2	S-HP1-HP2	95% confidence interval
CT (min)	−1.7 to 5.4	−0.7 to 6.4	−2.2 to 3.9	*−0.216°*	0.049	*0.412**	0.457	0.353	0.612	0.482	0.337 0.618
CFT (min)	−2.4 to 1.7	−3.7 to 2.9	−2.9 to 2.9	*0.270°*	*0.254°*	0.169	0.791	0.585	0.755	0.708	0.601 0.797
Alfa angle (°)	−7.7 to 17.3	−19 to 24.2	−22.7 to 18.2	*−0.297°*	−0.110	0.016	0.756	0.488	0.599	0.599	0.469 0.713
A10 (VCM U)	−8 to 7.3	−9.9 to 10	−8.9 to 9.7	0.133	0.109	0.159	0.894	0.846	0.877	0.871	0.815 0.914
A20 (VCM U)	−9.5 to 7	−10.6 to 10.1	−8.7 to 10.6	0.139	0.042	0.079	0.894	0.850	0.883	0.876	0.821 0.917
MCF (VCM U)	−10.8 to 6.4	−10.7 to 8.5	−8.5 to 10.6	*0.297°*	0.114	0.064	0.885	0.870	0.883	0.879	0.826 0.920
LI30′ (%)	−1.6 to 1.3	−1.7 to 1.4	−0.7 to 0.6	−0.012	−0.031	−0.031	0.159	0.160	0.740	0.289	0.138 0.448
LI45′ (%)	−6.2 to 4.2	−6.6 to 3.9	−3.5 to 2.7	−0.052	−0.089	0.021	0.558	0.493	0.797	0.605	0.476 0.718

A10: Amplitude at 10 min; A20 amplitude at 20 min; CFT: clot formation time; CI: confidence interval; CT: clotting time; HP1: heel prick blood sample by metal capillary; HP2: heel prick blood sample squeezed; ICC: intra-class correlation coefficient; MCF: maximum clot firmness; LY30: lysis index at 30 min; LY45: lysis index at 45 min; S: standard blood sample; U: units; VCM: viscoelastic coagulation monitor. $^{*}p < .001$; $^{\circ}p < .05$.

Blood sampling in neonates can be a difficult task, especially in preterm infants. Venipuncture is considered the method of choice for routine blood sampling in term neonates [15]. However, the neonate has a limited number of sites that can be used for arterial or venous sampling, and these must be preserved for premature and critically ill infants with ongoing needs for maintenance fluids, parenteral nutrition, or intravenous drug administration. Blood sampling from a central line requires discarding a significant initial blood volume to obtain an unaltered sample for testing, which may be unacceptable in extremely preterm infants. Significant fluctuations in cerebral oxygenation and blood volume are possible with blood sampling from umbilical arterial and vein catheters as peripheral arterial catheters in the very low birthweight infants [3–5]. Blood sampling from a peripherally inserted central catheter is generally not as feasible and effective as in children [16] and potentially burdened with higher rates of occlusion and/or mechanical complications due to the small gauge of the catheters. Indwelling arterial cannula can be used in the sickest term infants, but the risks of sepsis, blood loss, and vessel perforation must be weighed against the benefits of this procedure being used on a routine basis for all infants in intermediate or intensive care units. It is therefore understandable why capillary blood sampling is the most commonly used collection technique for routine laboratory tests that require a small amount of blood [6,7].

The results of our study confirm that VCM analysis can be performed in the newborn using a small amount of native blood by heel prick blood sampling. The VCM test performed on blood samples from both heel-pricking techniques showed strong to almost perfect agreement for VCT blood variables except CT, which was moderate because of the shorter time of coagulation activation in the HP2 blood sample. The best agreement between standard and heel-pricking blood sampling techniques was between S and HP1 blood samples. In this case, VCT blood variables showed moderate to almost perfect agreement except CT and LY30 index that were fair and poor, respectively. While the poor agreement for the LY30 index is explained by the lack of variability of the measurements, the greater reduction of the CT time in the heel prick blood samples appears to be attributable to an increase in tissue thromboplastin release compared to standard blood samples. This appears supported by the above-mentioned further reduction of CT time in the HP2 blood samples respect to the HP1. In our opinion, this result should not be considered a

Table 3. Overview and synthesis of results reported in Table 2.

	Lower and upper limits of agreement	ICC
CT (min)	Best for HP1-HP2	Fair agreement
CFT (min)	Best for S-HP1	Strong agreement
Alfa angle (°)	Best for S-HP1	Fair agreement
A10 (VCM U)	Best for S-HP1	Almost perfect agreement
A20 (VCM U)	Best for S-HP1	Almost perfect agreement
MCF (VCM U)	Best for S-HP1	Almost perfect agreement
LI30′ (%)	Best for HP1-HP2	Fair agreement
LI45′ (%)	Best for HP1-HP2	Moderate agreement

A10: Amplitude at 10 min; A20 amplitude at 20 min; CFT: clot formation time; CT: clotting time; HP1: heel prick blood sample by metal capillary; HP2: heel prick blood sample squeezed; ICC: intra-class correlation coefficient; MCF: maximum clot firmness; LY30: lysis index at 30 min; LY45: lysis index at 45 min; S: standard blood sample; U: units; VCM: viscoelastic coagulation monitor.

methodological drawback but rather as a strength of the VCT analysis performed on fresh untreated whole blood in conditions as similar as possible to those that trigger the coagulation cascade. Instead, this finding should be taken into account when constructing reference ranges for VCT blood variables with the VCM system in the neonatal period. Moreover, the almost perfect correlation between the standard blood sample and that of the heel prick with regard to the VCT blood variables that measure clot firmness means that the clot quality estimated by the VCM test is independent of the sampling technique.

The use of the VCM system proved to be simple and intuitive regardless of the blood collection technique used, without any technique limitation or the need for a particular learning curve. However, in the event of blood sampling from heel pricking, it is advisable both to respect adequate pre-warming of the heel (at least 2–5 min) as to use an automated device according to the infant's weight.

Conclusion

We demonstrated that the results of the VCT test performed with the VCM analyzer on blood sampling from the heel prick in neonates are comparable to those obtained by analyzing standard blood samples. We would like to encourage the use of this sampling technique in the construction of neonatal reference ranges with the VCM analyzer to obtain results more consistent with the true "*in vivo*" hemostatic function of these small patients.

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Disclosure statement

No potential conflict of interest was reported by the author(s).

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