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Comparison of capillary and venous blood sampling for routine coagulation assays

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ABSTRACT

Objectives: Capillary blood samples are generally assumed as unsuitable for coagulation testing since it is recognized that contamination with tissue factor and dilution with tissue fluid affects the coagulation assay. However, limited data is available about coagulations assays in which capillary blood sampling is compared to the standard venous blood withdrawal method. The aim of this study was to perform a method comparison between capillary and venous blood sampling for routine coagulation assays.

Methods: Both venous and capillary (finger stick) blood samples were collected from 188 healthy volunteers and patients. In citrate plasma, International Normalized Ratio (INR), prothrombin time (PT), activated partial thromboplastin time (APTT), thrombin time (TT), fibrinogen, and D-dimer were measured according to routine protocols using the ACL-TOP 750 LAS (Werfen) coagulation analyzer. Regression analysis was performed and the mean relative difference between capillary and venous sampling was reflected to the total allowable error (TEa).

Results: Strong correlations and acceptable variations, using the TEa as decision limit, were found for INR, PT, TT, fibrinogen, and D-dimer between capillary and venous sampling. However, capillary sampling resulted in significant shorter APTT values when using the standard APTT-SP Liquid reagent with a mean bias of −10.4% [95% CI −12.4 to −8.4].

Conclusion: Based on these results, capillary blood sampling proved to be an alternative blood withdrawal method for routine coagulation assays, with the exception of APTT, if a venipuncture is unavailable or undesired.

1. Introduction

Clinical laboratories offer a wide range of coagulation assays used in the diagnosis and management of patients with hemostatic disorders, preoperative screening, or anticoagulation therapy monitoring. The pre-analytical phase is an important factor in obtaining high-quality samples for coagulation testing, as the analysis of unsuitable specimens might lead to unreliable test results [1–3]. The standard blood sampling procedure at the hospital laboratory for coagulation testing is via venipuncture, which is in accordance with the international recommendation by Clinical and Laboratory Standards Institute (CLSI) H21-A5, the International Council for Standardisation in Haematology (ICSH), and laboratory medicine [4–6]. Capillary blood samples are generally recognized as unsuitable for coagulation testing. It is presumed to contain high levels of tissue factor shortening the clotting time, and dilution with tissue fluid may occur affecting the coagulation test outcome [7,8]. Point-of-care (POC) tests for monitoring of International Normalized Ratio (INR), like the CoaguChek®, were found to be suited for capillary blood samples [9–13]. More recently, new POC D-dimer assays have been introduced which need only a small volume blood sample obtained by a finger prick [14]. These tests are especially of interest where access to rapid laboratory tests is desirable, such as the general practitioners (GPs) office or anticoagulation clinics.

The request from clinicians for capillary blood collection for other routine coagulation test, such as International Normalized Ratio (INR), prothrombin time (PT), activated partial thromboplastin time (APTT), and thrombin time (TT), remains significant in particular from those involved in pediatrics. Capillary sampling offers a less invasive method for blood collection than venipuncture, which makes it more suitable for neonates, young children as well as for adult patients with poor venous access or severe anxieties concerning blood sampling [15,16]. Moreover, less blood volume is needed reducing the risk of anemia with frequent sampling, especially in newborns [17]. Studies have shown that patients prefer capillary blood sampling over venous sampling when frequent monitoring is required, as it was reported to be less painful [18].

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Limited data is available in which different blood sampling methods are compared to each other for their suitability in routine coagulation tests. The correlation between capillary and venous sampling for INR analysis has been evaluated in a small group of healthy volunteers and patients receiving oral anticoagulation therapy [19,20]. Interestingly, such relative simple and straightforward research cannot be found in literature for routine coagulation tests INR, PT, APTT, TT, fibrinogen, and D-dimer. The aim of the present study was to assess the agreement of capillary blood sampling (finger prick) in use for routine coagulation tests (including INR, PT, APTT, TT, fibrinogen, and D-dimer) as compared to the standard venous method for blood withdrawal.

2. Materials and methods

2.1. Subjects

Blood samples were collected from 44 healthy volunteers and 156 patients, presenting to the outpatient clinic of the Central Diagnostic Laboratory of the University Medical Center (UMC) Utrecht (Utrecht, The Netherlands) for routine coagulation tests, after giving written informed consent. 12 subjects were excluded from the study, because capillary samples were rejected due to premature clotting (9 times) or under filling of the tube (3 times). In total 102 men and 86 women with a median age of 59 years (range 18–85 years) were included. An overview of the study population characteristics is presented in Table 1 and detailed information specified per coagulation test in Supplementary Table 1. The number of subjects included complies with CLSI evaluation protocol EP9 [21]. The study was performed under the tenets of the Helsinki Declaration (as revised in 2013) and all relevant national regulations and institutional policies. The study protocol was approved by the authors' Institutional Review Board (METC 20–676/C).

2.2. Sample collection

Venous blood sampling was performed via venipuncture with the BD Vacutainer® blood collection system (Becton Dickinson, NJ, USA), at the cubital fossa and collected in citrate tubes (9NC Coagulation 3.2% sodium citrate, 3.5 or 2 mL, Vacuette®, Greiner Bio-One GmbH, Kremsmünster, Austria). In addition to the venipuncture, capillary blood samples were obtained by the finger stick technique. If necessary, the skin site was warmed before the puncture with a hot pack of 42 °C for maximal 3 min. First, the puncture site was cleaned with a tissue containing isopropyl alcohol 70% and allowed to dry. The skin was punctured using a BD Microtainer® contact activated lancet (Becton Dickinson, NJ, USA) to a depth of 2.0 mm and the first drop of blood was wiped off. The finger was gently squeezed to produce blood drops, which were collected into citrate microtubes (9NC Coagulation 3.2% sodium citrate, 0.5 or 1 mL, MiniCollect®, Greiner Bio-One GmbH, Kremsmünster, Austria). The microtubes were gently swerved during collection to facilitate mixing with the anticoagulant. After collection, tubes were capped and inverted four times to fully mix.

2.3. Coagulation assays

All samples were centrifuged for 5 min at 2980 x g at room temperature. In citrate plasma, International Normalized Ratio (INR), prothrombin time (PT), activated partial thromboplastin time (APTT), thrombin time (TT), fibrinogen, and D-dimer were measured according to routine protocols using ACL-TOP 750 LAS (Werfen, MA, USA) coagulation analyzer at the UMC Utrecht Central Diagnostic Laboratory. The precision of the coagulation assays over the course of the study is specified per test in Supplementary Table 2. Measurements were performed using designated reagent for INR (PT Owren, Technoclot, Technoclone, Vienna, Austria), PT (ReadiPlasTin, HemosIL, Werfen, MN, USA), TT (Thrombin Time, HemosIL, Werfen, MN, USA), fibrinogen (Q.F.A. Thrombin, HemosIL, Werfen, MN, USA), and D-dimer (D-dimer HS 500, HemosIL, Werfen, MN, USA). APTT was measured using two different types of reagent, including APTT-SP Liquid (HemosIL, Werfen, MN, USA) and SynthAFax (HemosIL, Werfen, MN, USA). Paired venous and capillary blood samples were processed and analyzed simultaneously on the same coagulation analyzer.

2.4. Statistical analysis

Data were analyzed using EP Evaluator® (Data Innovations, VT, USA, version 12.2). Outliers were computed using Deming standard error of estimate (SEE) of the regression. If the distance from the point to the regression line is more than 10x the SEE, the point was identified as an outlier. In addition, INR values above 4.5 were considered as outliers as well, since the reliability of these values is uncertain [22,23]. In this study outliers were identified in three assays, namely INR (0.6% of data points), PT (0.6% of data points), and D-dimer (5.2% of data points). For Deming regression and calculation of the mean difference, the outliers were excluded in the analysis. The mean relative difference between capillary and venous sampling of each coagulation test included was reflected to the total allowable error (TEa) obtained from literature [24,25]. For INR and TT the biological variation was not reported and was therefore obtained from another article [26]. The TEa is calculated according to the following formula: $0.25 \times (CV_i^2 + CV_g^2)^{0.5} + 1.65 \times 0.5 \times CV_i$, in which CV_i describes the coefficient of variation within a subject and CV_g the coefficient of variation between subjects [25].

3. Results

3.1. Regression analysis

A strong correlation between capillary and venous sampling was found for INR and PT using Deming regression (Fig. 1A-B). For both coagulation tests, the 95% confidence interval (CI) of the slope and intercept contains 1 and 0, respectively, indicating the absence of proportional and systematic differences. In addition, a correlation coefficient (R) of 0.98 and 0.99 was found for INR and PT, respectively.

Regression analysis showed a slope of 0.79 [95% CI 0.70 to 0.90] with a R value of 0.81 for APTT-SP Liquid (Fig. 1C). These results indicate a significant proportional difference, where capillary sampling resulted in shorter APTT values. No significant differences were found

Table 1
Overview of study population characteristics.

	Total (n = 188)
Age (years)	
median	59
range	18–85
Sex	
female	86 (46%)
male	102 (54%)
Healthy volunteers	41 (22%)
Patients	147 (78%)

Table 2
Mean difference (%) with 95% confidence interval (CI) per coagulation assay reflected to the total allowable error (TEa).

Assay	Mean difference (%) [95% CI]	Exceeding TEa?
INR	−0.1 [-1.3 to 1.0]	no
PT	−0.6 [-1.3 to 0.2]	no
APTT-SP Liquid	−10.4 [-12.4 to −8.4]	yes
APTT-SynthAFax	−4.0 [-5.1 to −2.8]	no
TT	−1.7 [-2.4 to −1.0]	no
Fibrinogen	−3.7 [-5.7 to −1.6]	no
D-dimer	1.2 [-7.6 to 10.0]	no

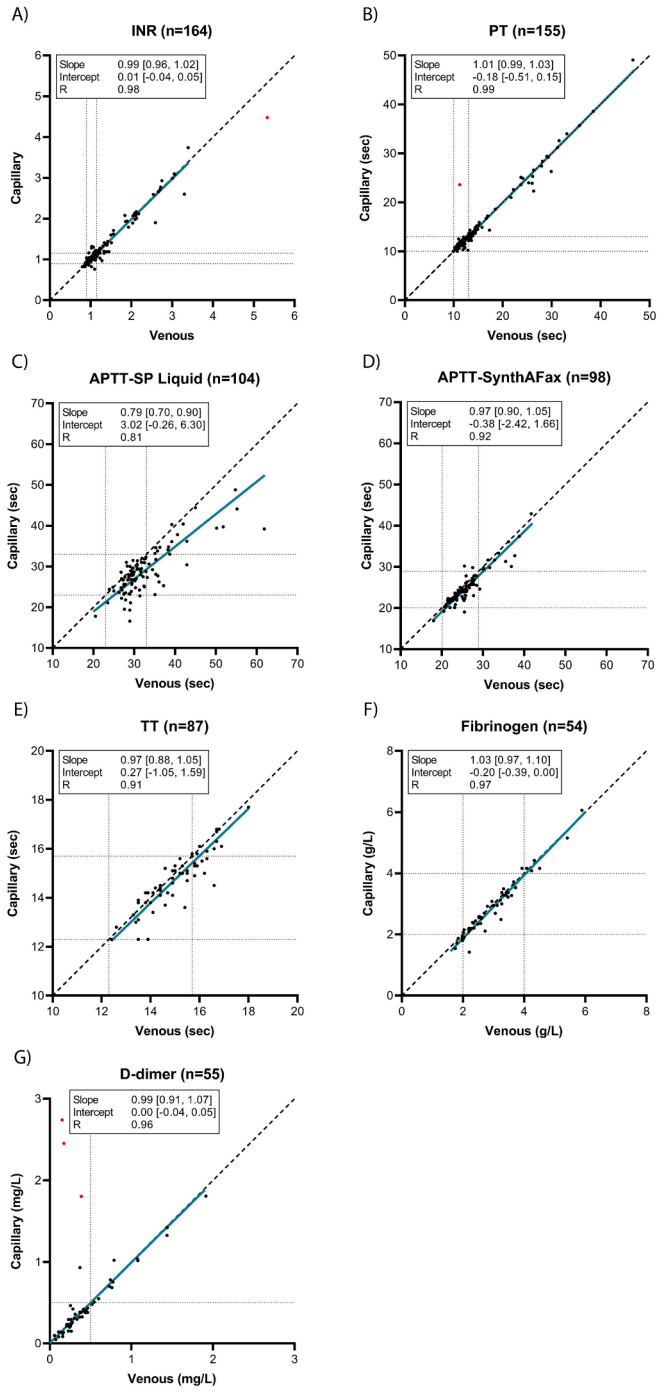

Fig. 1. Scatter plots of international normalized ratio, INR (A), prothrombin time, PT (B), activated partial thromboplastin time, APTT (C-D), thrombin time, TT (E), fibrinogen (F), and D-dimer (G). Correlation between capillary and venous sampling with the line of regression (solid line) and the line of equality (dashed line). Deming regression was used to analyze the linear regression, and slope and intercept are reported with 95% CI. Outliers (red dots) were excluded in the analysis. The vertical and horizontal dotted lines represent reference intervals as used by the Central Diagnostic Laboratory of the UMC Utrecht. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

for the intercept. When using the SynthAFax reagent, no significant differences for slope and intercept were found between capillary and venous sampling (Fig. 1D). The correlation between APTT-SP Liquid and APTT-SyntAFax with venous or capillary samples can be found in Supplemental Fig. 2.

Regression analysis of TT, fibrinogen and D-dimer showed no significant deviations of the slope and intercept with strong correlation coefficients of 0.91, 0.97 and 0.96, respectively (Fig. 1E-G).

3.2. Bias analysis

To study the bias, the relative and absolute difference between capillary and venous sampling was plotted against the reference sampling method (Fig. 2 and Supplementary Fig. 1). An equal distribution around zero was considered the optimal result, while one-sided distribution on either side of zero was considered to be a sign of an undesirable trend. The mean relative difference of INR and PT was −0.1% [95% CI −1.3 to 1.0] and −0.6% [95% CI −1.3 to 0.2], respectively, showing minimal variation between capillary and venous sampling (Fig. 2A-B). A negative difference was found for both APTT reagents (-10.4% [95% CI −12.4 to −8.4] for APTT-SP Liquid and −4.0% [95% CI −5.1 to −2.8] for APTT-SynthAFax), indicating shortening of the APTT when capillary blood samples were used (Fig. 2C-D).

To further define whether the found variation is clinically acceptable, the TEa was selected as a decision limit (Table 2). Only for the APTT-SP Liquid the TEa was exceeded, demonstrating significantly higher bias for capillary sampling compared to venous sampling than acceptable. The mean relative difference of TT and fibrinogen was −1,7% [95% CI −2.4 to −1.0] and −3.7% [95% CI −5.7 to −1.6], respectively, but were considered acceptable variations using the TEa as a decision limit (Fig. 2E-F, Table 2). Finally, D-dimer showed a mean relative difference of 1.2% [95% CI −7.6 to 10.0], which fell within the range of acceptable variation (Fig. 2G, Table 2).

4. Discussion

The INR was determined following the Owren PT method, while for routine PT testing another reagent was used lacking the addition of coagulation factor V and fibrinogen. The strong correlation found in this study between capillary and venous sampling for INR and PT is in line with previous reports [27]. The correlation between capillary and venous sampling for INR analysis has been evaluated in a small group of healthy volunteers and patients receiving oral anticoagulation therapy. The authors concluded that the observed bias between capillary and venous sampling was not clinically relevant [19,20]. Moreover, since POC tests for monitoring of INR are widely accepted and validated, it was expected that capillary sampling would have minimal effect on both INR and PT assays.

Two different types of reagent were selected to determine the APTT, including APTT-SP Liquid and SynthAFax. The APTT-SP Liquid reagent is the standard method for APTT measurements, while the SynthAFax reagent is used in our hospital to determine the APTT ratio for monitoring unfractionated heparin therapy. Results from this study indicate a different level of sensitivity for pre-analytical factors between the two reagents since only the blood sampling method was varied. According to the manufacturer, the only differences between the reagents are the type of contact activator and the concentration calcium chloride used (0.025 M for APTT-SP Liquid and 0.020 M for SynthAFax). This minimal difference in calcium chloride concentration is unlikely to completely explain the observed difference between the two reagents. APTT-SP Liquid is based on a colloidal silica dispersion, while SynthAFax contains ellagic acid as a soluble plasma activator. The exact mechanism is unclear and further research is needed to fully elucidate the effect of these contact activators on APTT results. In addition, additional studies on the clinical use of the SynthAFax reagent for APTT measurements could potentially result in a suitable APTT reagent for analyzing capillary samples. Since methods and instrumentation vary in each laboratory, it would be interesting to study the effect of other types of APTT reagents in future research.

It must be noted that outliers were identified in the dataset of D-dimer. For all outliers, capillary sampling resulted in D-dimer values

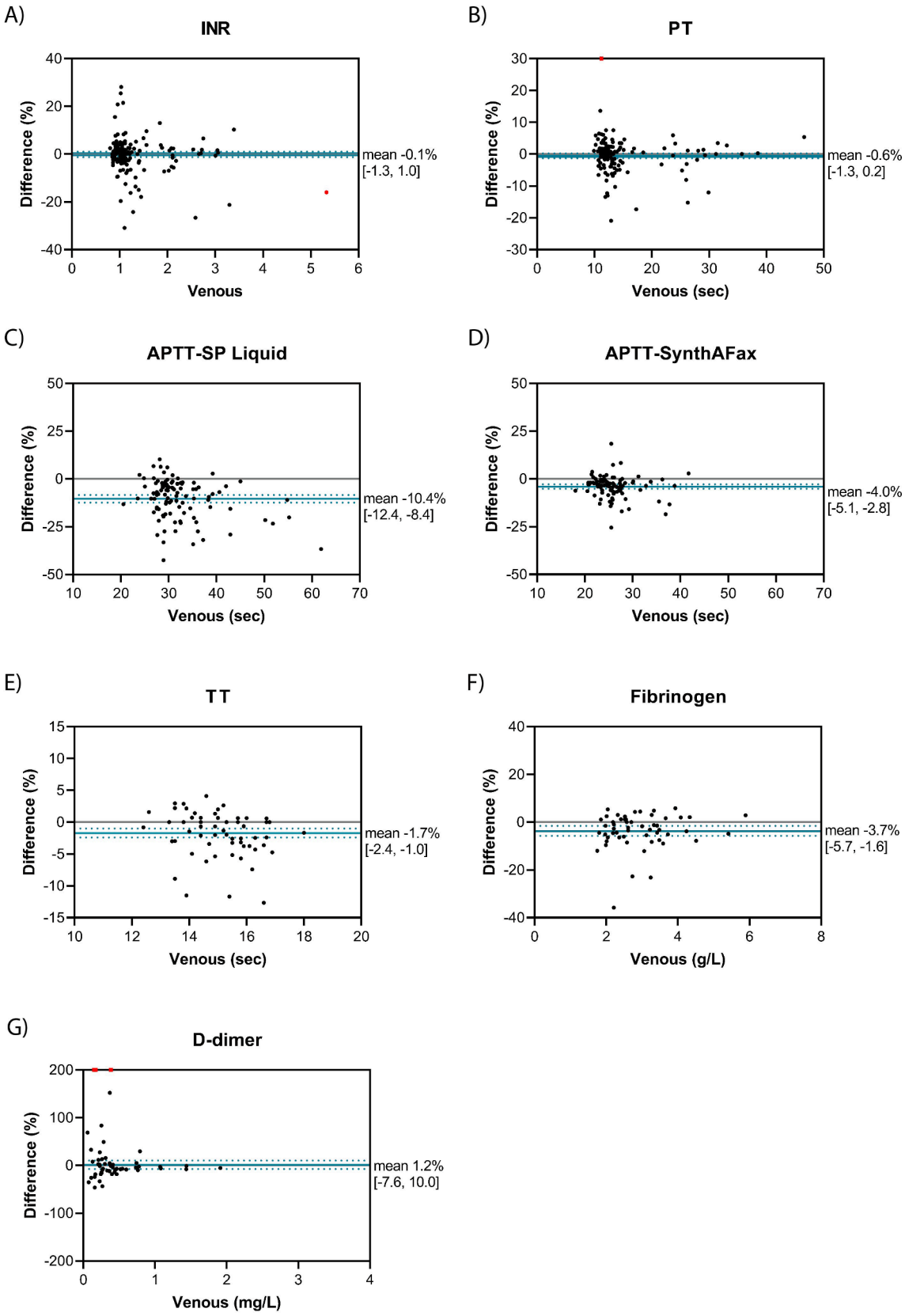

Fig. 2. Difference plots of international normalized ratio, INR (A), prothrombin time, PT (B), activated partial thromboplastin time, APTT (C-D), thrombin time, TT (E), fibrinogen (F), and D-dimer (G). The mean relative difference is plotted (solid line) with 95% CI (dotted lines). Outliers (red dots) were excluded in the analysis. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

above the cut-off point of 0.5 mg/L, while values lower than 0.5 mg/L were seen in the corresponding venous blood samples. This value (0.5 mg/L) was chosen as a cut-off point because it is universally used in the diagnostic strategy of clinically suspected deep vein thrombosis (DVT) or pulmonary embolism (PE) and has been confirmed in clinical studies [28,29]. Nevertheless, the opposite effect, which is clinically more relevant since patients can be missed, was not found. Practically this could imply that capillary D-dimer results below the cut-off point of 0.5 mg/L are considered reliable, whereas capillary D-dimer results above the cut-off require an additional sample via venipuncture. The D-dimer assay is a turdibimetric immunoassay based on polystyrene latex particles coated with monoclonal antibodies specific for D-dimer which cause agglutination upon binding. Preliminary activation of the coagulation cascade due to capillary blood sampling is therefore expected to play a minimal role. There was no information on possible interferences, such as medication or underlying disease, which could help explain in the identified outliers.

The rationale to reject capillary blood samples for coagulation testing is based on the preliminary activation of the coagulation cascade. Contamination with tissue factor during skin puncture and milking of the finger could lead to activation of coagulation and subsequently shorter coagulations times. Furthermore, dilution with tissue fluid due to milking could affect the coagulation test outcome as well [5,7,8]. Studies showed indeed that capillary (finger prick) sampling with milking resulted in a significant but small release of tissue factor. Nevertheless, there was no correlation found between capillary-venous differences in tissue factor and the effect on prothrombin time [8,30]. For routine collection of a capillary sample, it is usually crucial to wipe away the first drop of blood since this is most likely to contain excess tissue factor, which is also in accordance with the recommendations by CLSI GP42-A6 [17]. Therefore it is recommended that only specially trained personnel performs capillary blood sampling.

In conclusion, a method comparison between capillary and venous blood sampling for routine coagulation assays was performed in this study. Strong correlations and acceptable variations were found for INR, PT, TT, fibrinogen, and D-dimer between capillary and venous sampling. However, capillary sampling resulted in significantly shorter APTT values when using the standard APTT-SP Liquid reagent. Based on these results, capillary blood sampling proved to be an alternative blood withdrawal method for routine coagulation assays, with the exception of APTT, if a venipuncture is unavailable.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.clinbiochem.2022.01.010.

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