

Factor VIII, IX, and XI measurement by one-stage clotting assay with silica clotting time confirm reagent: a clinical laboratory helpful tool in the presence of lupus anticoagulant

Dosaje de factores VIII, IX y XI en un ensayo coagulable en una etapa utilizando reactivo de tiempo de sílica confirmatorio: una herramienta clínicamente útil ante la presencia de anticoagulante lúpico

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Abstract

Introduction: In clinical practice, coagulation factors levels measurement is used to detect possible factor deficiency in patients with bleeding manifestations or to explain the origin of prolonged routine coagulation tests results. **Objectives:** The aim was to evaluate factor VIII (FVIII), factor IX (FIX), and Factor XI (FXI) assay performed with silica clotting time confirm (SCTC) reagent in LA positive (LA+), normal controls (NC), and factors deficient (D) samples. **Materials and methods:** Citrated plasmas: 73 LA+, 45 NC; 77 D: 40 FVIII, 22 FIX, and 15 FXI. FVIII, FIX, and FXI D. (1) SynthASil activated partial thromboplastin time (APTT) (SYNT); (2) SCTC (3) FVIII chromogenic assay (FVIIICHROM). **Results:** NC: slightly lower FVIII SCTL than FVIII SYNT and FIX SYNT than FIX SCTL. No differences FIX SYNT versus FIX SCTL. D: No differences between FVIII SCTL, FVIII SYNT, and FVIII CHROM, or FIX SYNT versus FIX SCTL. FIX SYNT is slightly higher than FIX SCTL. NC+C: FVIII, FIX and FXI SCTL-SYNT $r > 0.970$. LA+: 36.7% FVIII SYNT, 66.1% FIX SYNT, and 86.2% FXI SYNT nonparallel dilution curves. FVIII SYNT1/40, FVIII SCTL, and FVIII: CHROM comparable results. FVIII SCTL-FVIII CHROM, $r: 0.949$, FVIII SCTL-FVIII SYNT, $r: 0.759$. Low FIX SCTL-FIX SYNT, no correlation FIX SCTL-FIX SYNT. **Conclusion:** FVIII, FIX, and FXI assays with SCTC seem to be useful to measure factor levels in LA+ samples.

Keywords: Coagulation factors dosage. Lupus anticoagulant. Silica clotting time confirm.

Resumen

Introducción: En la práctica clínica, la medición de los niveles de los factores de coagulación se utiliza para detectar posibles deficiencias de factores en pacientes con manifestaciones hemorrágicas o para explicar el origen de resultados prolongados en las pruebas rutinarias de coagulación. **Objetivo:** Evaluar dosajes de FVIII, FIX y FXI con Sílica Clotting Time Confirm (SCTL) en muestras anticoagulante lúpico-positivas (LA+), controles normales (CN) y deficientes de factores (D).

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Materiales y métodos: *Plasmas citratados: 73 LA+, 45 CN y 77 D: 40 FVIII, 22 FIX y 15 FXI. Dosaje FVIII, FIX y FXI: (1) APTT-SynthASil (SYNT); (2) SCTC (3) FVIII Cromogénico (FVIII CHROM). Resultados: CN: FVIII SCTC ligeramente inferiores a FVIII SYNT y FIX SYNT a FIX SCTC. FXI SYNT-FXI SCTC comparables. D: Sin diferencias FVIII SCTC, FVIII SYNT y FVIII CHROM, ni FXI SYNT versus FXI SCTC. FIX SYNT ligeramente superior a FIX SCTC. CN + D: $r > 0.970$ FVIII, FIX y FXI SCTC-SYNT. LA +: curva de dilución no-paralela 36.7% FVIII SYNT, 66.1% FIX SYNT y 86.2% FXI SYNT. FVIII SYNT1/40, FVIII SCTC y FVIII CHROM comparables. FVIII SCTC-FVIII CHROM $r = 0.949$, FVIII SCTC-FVIII SYNT $r = 0.759$. Baja FIX SCTC-FIX SYNT y no correlación FXI SCTC-FXI SYNT.*

Conclusión: *Los ensayos de FVIII, IX and XI con SCTC parecen útiles en muestras LA+, especialmente cuando se necesitan altas diluciones.*

Palabras clave: *Dosaje de factores de coagulación. Anticoagulante lúpico. Tiempo de Silica confirmatorio.*

Introduction

In clinical practice, coagulation factors levels measurement is used to detect possible factors deficiency in patients with bleeding manifestations, or to explain the origin of prolonged routine coagulation tests results. Particularly important are the intrinsic pathway factors assays, due to the highly prevalent severe bleeding disorders like hemophilia A, factor VIII (FVIII) deficiency, and B, factor IX (FIX) deficiency not only for the diagnosis but also for replacement therapy monitoring. FVIII is also important for von Willebrand disease diagnosis, and Factor XI (FXI) for diagnosis and therapy monitoring of FXI deficiency¹. The most widely available assay is the clotting one-stage method based on activated partial thromboplastin time (APTT) assay performed on a patient plasma dilution (PD) and factor-specific deficient plasma mixture¹⁻³. It is recognized that different APTT reagents (phospholipid [PL] origin, composition, and concentration, and intrinsic pathway activator) show different sensitivity to specific factor levels as well as to the presence of lupus anticoagulant (LA) activity in plasma. The presence of LA leads to false low levels factors due to the interference of LA on the PL availability for the APTT test used in the assay. It is suggested that APTT reagent used for factor assays should contain a high PL concentration and be low sensitivity to LA⁴. It has also been recommended that factor assays must be performed by processing in at least three patient PD and analyzing results by the parallel-line method in order to obtain a more accurate result and also to detect and overcome interferences like LA^{1,5}. Other techniques have been suggested to eliminate LA interference in factors activity measurements like neutralization of LA interference by adding hexagonal phase PL to patient plasma previous factor testing⁶, use of heterophilic factor deficient plasmas instead of human deficient ones⁷, or using amidolytic or chromogenic (CHROM) assay^{1,8}. Of these, CHROM methods are available in many hemophilia centers but not in clinical laboratories.

Depending on the characteristics and concentration of antibodies, many LAs generate a very long prolongation in APTT and could interfere with factor dosing even at 1:40 PD (the highest dilution performed automatically by some coagulometers), causing falsely low results that force the process several additional PD to reach the actual factor level with less accurate results.

Some authors have been reported that using confirmatory (high PL) silica clotting time confirm (SCTC) reagent in assays for intrinsic pathways factors could be a good and easy tool to overcome LA effect⁹.

The present study aimed to evaluate FVIII, FIX, and FXI assay performed with an APTT, which contains silica as activator and high PLs concentration (SCTC) in a large number of LA positive samples as well as in normal controls (NC) and factors deficient plasmas in three different laboratories to verify the previously reported study.

Materials and methods

Population

A total of 195 samples were evaluated. Samples and controls evaluated are listed in [table 1](#). The study was performed by three different hemostasis laboratories from different hospitals: 1-Hospital Italiano de Buenos Aires, 2- Unidad Asistencial Por más salud Dr, César Milstein, 3-Hospital Británico de Buenos Aires, all in Ciudad Autónoma de Buenos Aires, Argentina. LA positive samples were mainly from center 1, samples from congenital deficient patients were collected in all three centers, but hemophilia A (HA) samples were mainly from center 2. The protocol was revised and approved by the Institutional Review Board on human subject research of the Hospital Italiano de Buenos Aires Ethics Committee (CEPI). No written consent was required because the study fulfilled the established criteria for handling shed blood samples and, patients' data were collected retrospectively, identifiers were removed, and data used was anonymous.

Table 1. Study and control groups description

LA+		NC	FVIIIID		FIXD		FXID	
Description	n	n	Description	n	Description	n	Description	n
Total	73	45	Total	40	Total	22	Total Congenial deficient total	15
LA+	60		HA	30	Mild HB	6	Severe	8
LA+AVK	13		Severe HA	11	Vitamin K deficient	2	Moderate	1
			Moderate HA	9	AVK	14	Mild	6
			Mild HA	10				
			VWD	6				
			Acquired HA	4				

LA+: lupus anticoagulant; NC: normal controls; FVIIIID: factor VIII deficiencies; FIXD: factor IX deficiencies; FXID: factor XI deficiencies; AVK: vitamin K antagonists; HA: hemophilia A; HB: hemophilia B; VWD: von Willebrand disease.

Blood sampling

Blood was drawn by clean venipuncture and collected in vacutainer tubes containing 1/10 volume of sodium citrated (Becton Dickinson). Platelet-poor plasma was obtained by centrifugation at room temperature of 200 g for 10 min. A second plasma centrifugation was performed, and samples were divided into 2 aliquots: One was processed as per the physician's request, and the other was kept frozen at -70°C until used for the study (no more than 3 months).

Coagulation tests

For APTT assay: HemosIL APTT SP (Werfen).

The two methods used for factor dosages were performed using FVIII, IX, and XI immune deficient plasmas and HemosIL Calibrator Plasma, both from Werfen.

- Standard method: FVIII SYNT, FIX SYNT, and FXI SYNT dosage in 3 PDs (1/10, 1/20, and 1/40), using HemosIL SynthASIL APTT reagent (Werfen). All laboratories used two levels of internal controls (normal and low) (HemosIL NC assayed and HemosIL special test 2 control, Werfen and participated in an external proficiency program).
- Alternative methods FVIII SCTC, FIX SCTC, FXI SCTC: 1/10 PD, HemosIL SCT confirm (SCTC) as APTT reagent, and HemosIL SCT CaCl_2 both from Werfen. The method was validated using two levels of internal controls and compared with the previous method.
- FVIII CHROM assay (FVIII: CHROM): Electrachrome FVIII Kit (Werfen) containing bovine FIXa 0,3 U/vial, FX in excess 2,7 IU/vial and Thrombin 1 UNIH/vial, CaCl_2 40 μmol /vial and PLs 0.2 μmol /vial). CHROM

substrate: S-2765 7,7 mg/vial with thrombin synthetic inhibitor I2581 and mannitol reconstituted in tampo-nade 25mM TRIS.

All coagulation tests were performed in ACL TOP family coagulometers: ACLTOP 500 (Werfen).

Statistics

Friedman and Wilcoxon pared non-parametric tests. Correlations were performed by the Spearman Rank method. Statistics performed by IBM Statistical Package for the Social Sciences 23 software.

Results

Analytical inter-assay coefficient of variation for SCTC methods were: FVIII 4.5% and 6.3%, FIX 4.9% and 7.0%, FXI 4.7% and 6.1% comparable to that observed by the original assay used in (SYNT): FVIII 4.5% and 3.5%, FIX 5.2 and 4.7%, FXI 5.3 and 8% for normal and low abnormal controls, respectively.

Comparison of FVIII, FIX, and FXI levels measured between SYNT and SCTC methods in NC and factor deficiencies

Table 2 shows the results of FVIII, FIX, and FXI obtained by different methods NC, as well as FVIIIID, FIXD, and FXID (control samples). In NC, FVIII SCTC showed statistically slightly lower values than FVIII SYNT without clinical significance. In the case of samples from FVIIIID, no statistical differences were observed between FVIII SYNT and FVIII SCTC (Fig. 1). All NC

Table 2. FVIII, FIX and FXI levels measured in LA + samples and control groups

Sample type	FVIII SYNT (IU/dL) 1/10 Median (IQR)	FVIII SYNT (IU/dL) 1/40 Median (IQR)	FVIII SCTC (IU/dL) 1/10 Median (IQR)	FIX SYNT (IU/dL) 1/10 Median (IQR)	FIX SYNT (IU/dL) 1/40 Median (IQR)	FIX SCTC (IU/dL) 1/10 Median (IQR)	FIX SYNT (IU/dL) 1/40 Median (IQR)	FXI SYNT (IU/dL) 1/10 Median (IQR)	FXI SYNT (IU/dL) 1/40 Median (IQR)	FXI SCTC (IU/dL) 1/10 Median (IQR)
Normal controls	130 (103-161)		113* (100-137)	106 (92-120)		113* (100-127)	106 (98-139)			105 (100-127)
LA +	97 (79-128)	109 [‡] (84-140)	106 [§] (89-126)	59 (25-84)	83 (59-105)	102 [¶] (87-115)	46 (20-98)		83** (49-118)	105** (93-118)
FVIIIID	3.6 (0.9-32.6)		4.8 (1.1-28.9)							
FIXD				37 (24-44)		32 ^{††} (19-45)				
FXID								1.0 (1.0-15.0)		1.4 (0.0-11.5)

*p = 0.002 FVIII SYNT 1/10 versus FVIII SCTC 1/10.

†p = 0.041 FIX SYNT 1/10 versus FIX SCTC 1/10.

‡p < 0.001 FVIII SYNT 1/10 versus 1/40.

§p = 0.046 FVIII SYNT 1/10 versus FVIII SCTC 1/10; and p < 0.001 FIX SYNT 1/40 versus FIX SYNT 1/10 and FIX SCTC 1/10 versus FIX SYNT 1/10.

¶p = 0.001 FIX SCTC versus FIX SYNT 1/40.

**p < 0.001 FXI SYNT 1/10 versus FXI SYNT 1/40 and FIXSCTC 1/10 versus FXI SYNT 1/10.

††p = 0.011 FIX SCTC 1/10 versus FIX SYNT 1/10.

LA: lupus anticoagulant; FVIIIID: FVIII deficient; FIXD: FIX deficient; FXID: interquartile range.

and D plasmas presented parallel dilution curves (DC) compared to normal plasma. FIX SCTC presented statistically slightly higher values than FIXSYNT in NC but statistically lower values in FIX deficient (Table 2 and Fig. 2A), without clinical significance in both cases. There were no differences between FIXSYNT and FXI SCTC in NC nor in FXI deficient (Table 2, Fig. 2B). The correlation between SCTC and SYNT methods considering normal and deficient plasmas were 0.975, 0.977, 0.995 for FVIII, FIX and FXI, respectively, as well as between FVIII SCTC and FVIII: CHROM, 0.968, p < 0.001 for all correlations.

Comparison of FVIII, FIX, and FXI levels measured between SYNT and SCTC methods in patients with positive LA

Factors dosages performed with SYNT at three PD s in LA+ samples showed nonparallel DC in 36.7% of FVIII, 66.1% of FIX, and 86.2% of FXI.

There were 5/62 LA+ samples that showed FVIII SYNT 1/10 results < 50 IU/mL, all of them became > 50 IU/mL by FVIII SYNT 1/40, and the 62 presented normal or increased results by FVIII SCTC. Considering FIX SYNT 1/10 23/58 LA + samples analyzed presented values < 50 IU/mL, and 14/23 persisted low by FIX 1/40, being low by FIX SCT only 5/14 samples from patients under AVK treatment with INR > 3.0. In the analysis of FXI SYNT 1/10 18/30 LA+ samples presented results < 50 IU/mL and 8/18 persisted low by FXI SYNT 1/40, but all of them were normal by FXI SCTC.

Figure 1 shows all results from LA+ samples (both with parallel and nonparallel DC). In a smaller group of samples studied at the hemophilia center no statistically significant differences were found between FVIII SYNT, FVIII CHROM, and FVIII SCTC in NC and HA patients, nor in LA+ (only 4/15 presented nonparallel DC with FVIII SYNT), (Table 3 and Fig. 1).

Figure 2 shows bland altman graphs comparing FIX and FXI by SCTC and synth. In LA+ samples FIX SYNT 1/10 presented lower levels compared to FIX SYNT 1/40 and FIXSCTC. Even more, FIX SYNT 1/40 was lower than FIXSCTC (Table 2). This is clearly observed in Fig. 2C where some samples do not achieve normal values of FIX even at 1/40 dilution.

FXI SYNT 1/10 presented statistically lower results than FXI SYNT 1/40 and FXI SCTC in LA + samples, particularly those with non-parallel DC (Table 2, Fig. 2D).

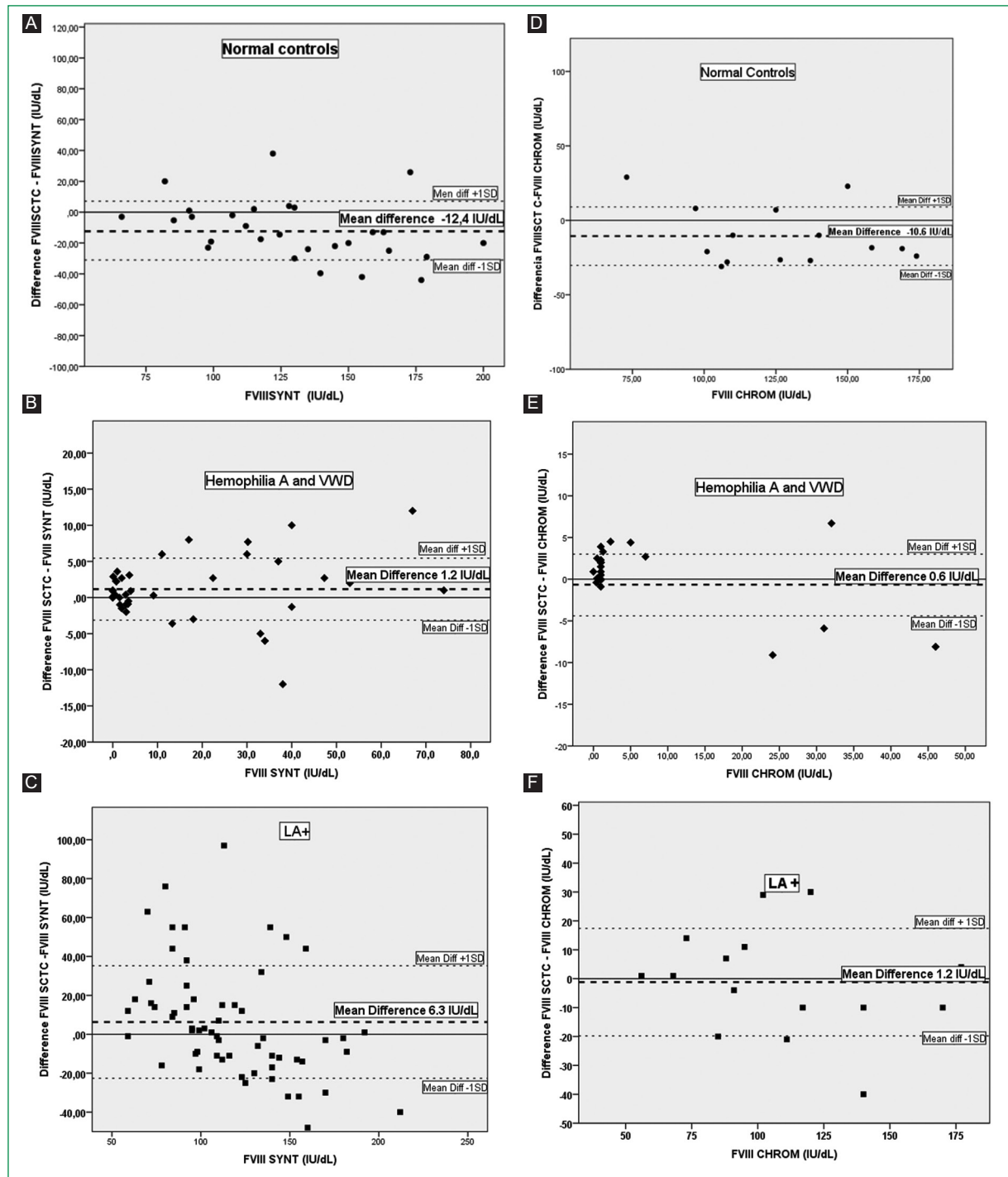


Figure 1. A: bland altman graphs comparing FVIII SCTC versus FVIII Synth in normal controls (NC), B: hemophilia A and von Willebrand Disease (VWD) patients, C: and lupus anticoagulant (LA) +, D: as well as FVIII SCTC versus FVIII CHROM in NC, E: hemophilia A and VWD patients and F: LA +.

Correlations between FVIII performed by SYNT and SCTC methods were better when using 1/40 PD than 1/10 PD in LA+ plasmas 0.759 versus 0.602 ($p < 0.001$ for both) but were really good between FVIII SCTC and FVIII: CHROM (0.949, $p < 0.001$). There was no

correlation between SCTC and SYNT 1/10 PD methods for FIX and only low statistical correlation with SYNT 1/40 PD (0.373, $p = 0.004$) in LA+ plasmas. Even worse, there was no correlation SYNT and SCTC methods in FXI measurements.

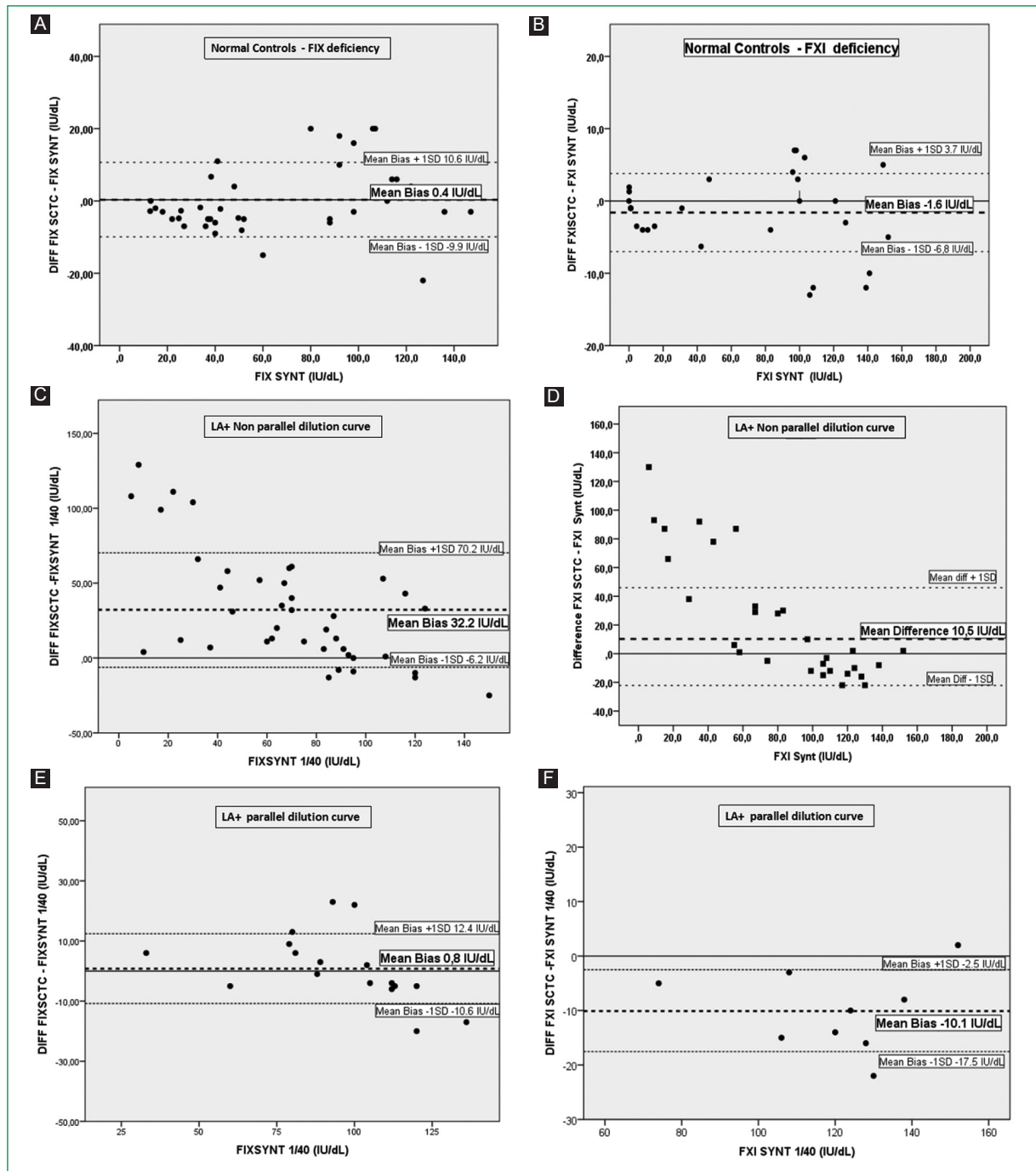


Figure 2. A: bland altman graphs comparing FIXSCTC versus FIX Synth in normal controls (NC) and FIX deficient, C: lupus anticoagulant (LA) + with non-parallel FIX Synth dilution curve (DC), E: and parallel FIX Synth DC, B: as well as FXISCTC versus FXI Synth in NC and FXI deficient, D: LA+ with non-parallel FXI Synth DC, F: and parallel FXI Synth DC.

In only two additional cases of patients presenting acquired HA and LA, coexisting both autoimmunity expressions, residual FVIII SCTC was higher than FVIII SYNT 1/40 PD, and in one patient, FVIII inhibitor titration was 1 BU lower with FVIII SCT than with FVIII SYNT.

Discussion

This study confirms that FVIII, FIX, and FXI levels could be measured with one stage clotting assay using an APTT reagent with silica as activator and high PL concentration (SCTC) in cases of LA + plasmas to

Table 3. FVIII measured by coagulometric standard (SYNT), alternative (SCTC) and chromogenic technics

Sample type	FVIII SYNT 1/10 Median (IQR)	FVIII SYNT 1/40 Median (IQR)	FVIII CHROM Median (IQR)	FVIII SCTC 1/10 Median (IQR)
Normal controls (n = 15)	126 (99-166)		126 (105-152)	108* (95-142)
LA + (n = 15)	101 (58-120)	109 (78-148)	102 (85-140)	95 (69-131)
FVIIIID (n = 25)		2.9 (0.4-11.2)	1.0 (1.0-6.0)	3.0 (0.9-9.5)

*p = 0.046 FVIII SCT1/10 versus FVIII CHROM.
LA: lupus anticoagulant; FVIIIID: FVIII deficient; IQR: interquartile range.

overcome LA interference and factor level underestimation avoiding results misinterpretation by clinicians. This is accordance with that previously published⁸ but in the present study, we used different standard APTT silica reagent and clot detection principle coagulometer. In addition, in the present study, a larger number of LA + and NC as well as FVIIIID, FIXD, and FXID samples were tested which allowed to confirm that factor deficiencies can be correctly identify. It is important to consider that FVIIIISCTC presented a very good correlation with FVIIIICHROM which is considered the ideal method to overcome LA interference.

One interesting observation is that the no parallelism in LA+ samples was less frequent in the dosage of FVIII than FIX and FXI showed by many FIXSYNT and FXISYNT low results even at 1/40 PD. This agrees with the results from Tang and Yin⁹, who, in the 12 LA+ samples found BIAS < 20% less using APTT A compared to SCTC in only 2 samples for FVIII but in 5 for IX and 4 for FXI, even with higher PD. The reason for this finding is not known, but it could be thought that in intrinsic tenase complex the Gla Domain and Calcium-dependent anchorage of FIX on PL surface is very important, and PL concentration-dependent and LA compete with the binding of coagulation factors for catalytic PL surfaces in coagulation tests like APTT¹⁰. Considering that it has been demonstrated that FIX a has lower affinity (higher kinetic dissociation constant) to PL surfaces than FVIII a when forming the Tenase complex¹¹, FIX activity test could be more sensitive to the limited availability of anionic PL in the reaction when LA is present. Additionally, FVIII is an acute phase reactant, and its levels are frequently high in patients with autoimmune disease and thrombotic primary antiphospholipid syndrome, situations that could lessen the effect of LA in the FVIII assay¹².

The present study has limitations such as the fact that factor assays studied only up to 1/40 PD, a common procedure in clinical laboratories. As a strength, this

study included not only NCs and LA+ plasmas but evaluated plasmas from patients with congenital or acquired factor deficiencies to evaluate SCTC factors methods and even more FVIIIISCTC was compared to FVIIIICHROM.

Conclusion

FVIII, FIX, and FXI levels could be measured with one-stage clotting assay by using SCTC in LA+ patients to overcome LA interference and avoid factor levels underestimation. This method could be a reliable tool when deficiencies or specific factor inhibitors are suspected in a patient with LA, particularly when a CHROM test is not available.

Funding

None.

Conflicts of interest

None.

Ethical considerations

Protection of humans and animals. The authors declare that no experiments involving humans or animals were conducted for this research.

Confidentiality, informed consent, and ethical approval. The authors have obtained approval from the Ethics Committee for the analysis of routinely obtained and anonymized clinical data, so informed consent was not necessary. Relevant guidelines were followed.

Declaration on the use of artificial intelligence. The authors declare that no generative artificial intelligence was used in the writing of this manuscript.

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