

# APPLICATION OF GLOBAL COAGULATION ASSAYS IN HEMOPHILIA B PATIENTS TO EVALUATE THE HEMOSTATIC POTENTIAL IN BASELINE CONDITIONS AND AFTER FIX CONCENTRATE ADMINISTRATION.

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**Introduction:** Hemophilia B (HB) patients (pts) show a variable bleeding phenotype. The severity of bleeding may be different in pts sharing the same FIX:C level. The basis for this heterogeneity is still poorly understood.

**Aim:** Application of global coagulation assays in HB pts, in baseline conditions and after recombinant FIX (rFIX) concentrate infusion, in order to explore the possible correlation between laboratory parameters and clinical outcome.

**Patients and Methods:** Severe/moderate HB pts were enrolled. Bleeding phenotype (BP) was defined as severe or mild considering the annual bleeding rate, orthopedic Gilbert score and mean annual consumption of FIX concentrate from the last 5 years. Thromboelastography (TEG) and calibrated automated thrombography (CAT) were performed before and after the infusion of 50 IU/kg of rFIX concentrate.

## CLINICAL FEATURES

Pt	FIX level (68-130%)	Mean ABR (last 5 years) All Bleedings/Joint bleedings	Orthopedic Score (0-72)	Mean Annual FIX concentrate UI/kg consumption (last 5 years)	Bleeding phenotype
1	4.5	0.4/0	0	890	Mild
2	4.3	0/0	0	74	Mild
3	0.9	0.4/2.4	10	400	Severe
4	0.7	1.6/0	1	298	Mild
5	0.4	1/12	9	1707	Severe
6	8.5	0.4/0.6	4	67	Mild
7	0.9	0.6/0.2	8	3419	Severe
8	10	1.6/1.4	6	648.74	Mild
9	3	3.4/0.2	0	4023	Mild

## CAT

Pt	FIX level (68-130%)	Bleeding phenotype	Lag Time (4.3 – 9.4 min)	ETP (379.2 – 909.5 nM x min)	Peak (27.1 – 90.6 nM)	tt-Peak (9.6-16.0 min)
1 Pre	4.5	Mild	4.7	155.1	7.6	17.1
1 Post	48.0		3.6	296.1	19.1	11.3
2 Pre	4.3	Mild	5.8	167.9	8.1	19.5
2 Post	77.0		8.3	234.3	15.4	15.5
3 Pre	0.9	Severe	10.0	89.2	4.2	28.0
3 Post	57.2		9.7	227.8	16.1	17.7
4 Pre	0.7	Mild	5.1	Not calculated	8.0	19.0
4 Post	40.1		5.6	181.9	10.3	14.6
5 Pre	0.4	Severe	14.0	Not calculated	3.5	45.2
5 Post	41.1		22.7	Not calculated	5.6	41.2

## Results:

• 9 HB patients were enrolled: 3 moderate (FIX:C 4.5%, 4.3% and 3% respectively, all mild BP) 4 severe (FIX:C<1%, 1 mild BP, 3 severe BP), and 2 mild (FIX:C 8.5% and 10% respectively, both mild BP).

• **TEG:** in baseline conditions, *R* (n.v.:4.3-6.3min) was increased inversely to the FIX:C levels (median *R*: 16.8min; range 7-25.9). Median *α-Angle* (n.v.: 57.21-70.76°) and *Maximum Amplitude* (n.v.: 59.77-70.51mm) were reduced: 43.4° (35.6-65.5) and 55.2mm (50.7-63.9) respectively. Just 2 moderate patients showed normal values for *α-Angle* and *Maximum Amplitude*. Lysis parameters (Ly30/60%) were increased in 2 severe patients with severe BP. After rFIX concentrate infusion, all TEG parameters showed an improvement: median *R* 8.2min (5.8-12.9), median *α-Angle* 59.2° (39.9-65), median *Maximum Amplitude* 62.1mm (56.2-69.2). Ly30/60% remained increased in the 2 severe patients.

• **CAT:** we have analyzed 5 patients, 2 moderate (FIX:C 4.5% and 4.3% respectively, both mild BP) and 3 severe (FIX:C<1%, 1 mild BP, 2 severe BP). In baseline conditions, *lag time* (n.v.:4.3–9.4min) was increased in 2 severe pts with severe BP (10 and 14 min, respectively) while was normal in 2 moderate (4.7 and 5.8 min) and in 1 severe patient with mild BP (5.1 min). Regarding *ETP*, *Peak*, *time to-Peak*, we found alterations in all patients. After rFIX concentrate infusion, we observed a normalization just for *time to-Peak* in moderate patients and in 1 severe patient with mild BP.

## TEG

Pt	FIX level (68-130%)	Bleeding phenotype	R (4.3 -6.3 min)	Alpha Angle (57.2 – 70.8 °)	MA (59.8 – 70.5 mm)	Ly30 (0.2 – 3.8 %)	Ly60 (3.1 – 14.6 %)
1 Pre	4.5	Mild	7.0	65.5	61.6	1.1	10.9
1 Post	48.0		6.2	62.9	61.3	1.2	12.4
2 Pre	4.3	Mild	10.7	58.1	63.9	1.8	9.1
2 Post	77.0		6.8	65.0	69.2	0.9	6.3
3 Pre	0.9	Severe	16.8	40.6	50.7	6.9	23.3
3 Post	57.2		5.8	62.3	56.2	4.0	19.7
4 Pre	0.7	Mild	25.9	39.4	55.2	3.9	14.6
4 Post	40.1		8.6	58.5	62.7	0.8	7.6
5 Pre	0.4	Severe	22.7	43.4	58.1	0.6	4.1
5 Post	41.1		7.3	64.6	64.1	2.0	7.6
6 Pre	8.5	Mild	18.6	48.6	55.7	0.9	8.8
6 Post	46.4		11.7	59.2	62.1	1	7.1
7 Pre	0.9	Severe	17.6	35.6	53.3	4.7	21.3
7 Post	42.2		12.9	39.9	58.4	5.2	18.6
8 Pre	10	Mild	14.1	40.2	54.2	0.5	4.4
8 Post	60.7		9.8	53.4	63.8	0	1.8
9 Pre	3	Mild	16.6	47.2	54.4	3.1	13.1
9 Post	48.2		8.2	53.1	59.5	2.1	9.8

**Conclusion:** In 9 patients, TEG parameters seemed not to be informative for BP, because related to the FIX:C level. Regarding CAT, performed in 5 patients, we found that *Lag time* could be informative for BP, because in baseline conditions was normal in the 3 patients with mild BP. Replacement therapy determined always at least an improvement on TEG/CAT parameters, related to an increase of FIX:C levels. These data need to be confirmed on a larger population.

