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Postoperative TGA monitoring of haemostasis of haemophilia patients with inhibitor (Second report)

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[Background and purpose] We announced the Postoperative TGA（TECHNOTHROMBIN®TGA） monitoring of haemostasis during peri-operative periods for patient with haemophilia with inhibitor (PWHWI) in the WFH of 2014. Our previous report showed that there is good relationship between activated partial thromboplastin time (APTT) and thromboelastography (TEG, Rotem®) as hemostasis monitoring. This time, we monitored haemostastis by three type of bypass agents during peri-operative periods for PWHWI using TGA. In addition, the results analyzed by up-graded software (GEN5 ; Ver2.06)) showed in this poster and discussed the possibility of haemostatic monitoring by TGA.

[Patient and method] A Patient with hemophilia A with inhibitors underwent revision total knee arthroplasty using three type of bypass agents (table 1). We monitored haemostasis by TGA. TGA was performed on plasma with RCL and RCH reagent (table 2) using the FLx800 Fluorescence Reader (Biotek). The lag time (min), the time to peak thrombin generation (time: min), the peak (peak: min), and the endogenous thrombin potential (ETP: nM·min) were evaluated. Before surgery, we evaluated the effect of two bypassing agents (aPCC and pd-FVII/FX) using TGA at before and 10 minutes after administration as pre-test.

[Pre-test Result] The results of pre-operative TGA of aPCC and Pd-FVII/FX showed graph 1 and 2 respectively. TGA curves of both bypassing agents were flat before administration and rise up after administration. All of four TGA parameters of pd-FVII/FX was better than those of aPCC (Graph 1-B,C and Graph 2-B,C)

[Haemostatic control plan] According to the pre-test results, we decided to use two bypassing agents sequentially as follows. Pd-FVIIa/FX was administrated every 36 hours and rFVIIa every three hours. When both bypassing agents need to administrate, rFVIIa was skipped and never administrated them at same time and we monitored haemostasis at two points before and 10 minute after administration (table 3). After day 8, aPCC was administrated every other day.

[TGA monitoring during surgery] In both graph 3 and 4, TGA curves before administration had already lower peak influenced by previous administration and all of four parameters became better after administration. We evaluated both bypass agents were effectiveness and no differences between them. Monitoring points were at Day7 and Day 8 (Table 3)

[Topics] Version up-graded TGA analyzed program GEN 5 Ver2.06 is able to draw new curve such as graph 1,2,3,4-A. This graph is the cumulative graph of relative fluorescence units. We weren't able to see the results until finished analysis completely before, however this up-graded program showed the graph in real time. At Graph 1,2 and 4-A, the effect of three type bypass agents showed clearly, but Graph 3-A couldn't show the differences between before and after administration.

[conclusion] We have some hemostatic monitor such as ROTEM and TGA, but they aren't good enough as monitor for PWHWI. We hope that TGA will be good monitoring tool by upgraded program so on.

(Table 1) [Bypass agents]

Novo Seven®	Recombinant activated VII (rFVIIa)	Novo Nordisk A/S,Bagsvaerd,Denmark
FEIBA®	Plasma-derived activated prothrombin complex concentrate (Pd-aPCC)	Baxter International
Byclot®	Complex concentrate of plasma-derived activated factor VII(FVIIa) and factor X (pd-FVIIa/FX) 1.2	Kaketsuken,Kumamoto,Japan

(Table 2) [TGA Reagent]

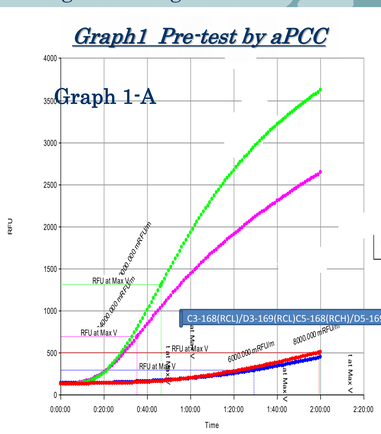
Reagent	purpose
TGA RC Low	- Measurement of thrombophilic tendency (preferentially with platelet poor plasma PPP) - Measurement of bleeding tendency - For monitoring FVIII inhibitor Bypass therapy with rFVIIa and FEIBA - hF VII, hF Xa, hF XIa - to monitor the thrombogenity of microparticles
TGA RC High	- for monitoring of anticoagulant therapy
TGA RD	- For monitoring heparin, direct thrombin and Xa inhibitor therapy - hF XIIa, plasma callicrein, callicrein1 (Tissue Factor)

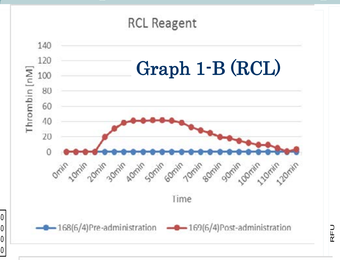
(Table 3) [Haemostatic control plan]

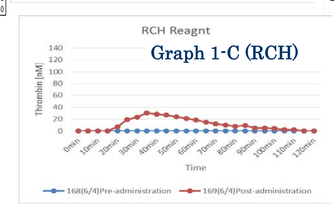
Table 3	Day 0	Day 1		Day 2		Day 3		Day 4		Day 5		Day 6		Day 7		Day 8	
Time (hr)	0	12	24	36	48	60	72	84	96	108	120	132	144	156	168	180	192	204
Interval (hr)	every three hours (q3h)																	
pd-FVII/FX	↓			↓			↓			↓			↓				↓	
rFVIIa		↓q3h			↓q3h			↓q3h			↓q3h				↓q3h			
Blood Exam Point															G3		G4	

[References]
1.Shirahata A, et al, *Haemophilia* 2012;18 : 94-101
2. Shirahata A et al, *Haemophilia* 2013 ; 19 : 330-7

Graph1 Pre-test by aPCC



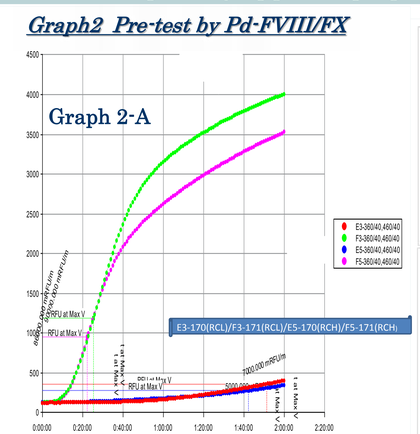


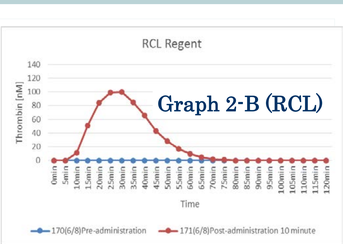


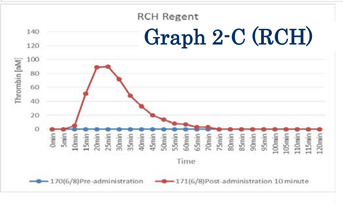
Well	Max V [360/40,460/40]	t at Max V [360/40,460/40]	Lagtime [360/40,460/40]
C3	8000	1:59:35	1:13:28
D3	50000	0:46:35	0:22:57
C5	6000	1:29:35	1:03:25
D5	34000	0:35:35	0:19:00

		Bypass agent	lag phase time [min]	peak height Thrombin [nM]	peak height time [min]	AUC
No168	RDL	Before	54.1	#DIV/0!	0.1	0.0
No169	RDL	After	15.1	43.4	46.6	2346.0
No168	RDH	Before	44.6	#DIV/0!	0.1	0.0
No169	RDH	After	13.1	30.6	34.6	1383.3

Graph2 Pre-test by Pd-FVIII/FX



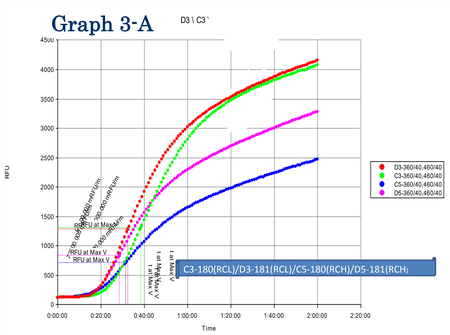


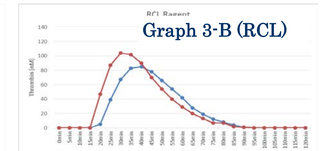


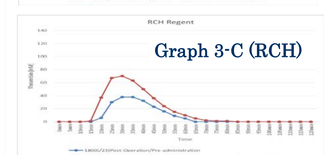
Well	Max V [360/40,460/40]	t at Max V [360/40,460/40]	Lagtime [360/40,460/40]
E3	7000	1:51:35	1:17:48
F3	90000	0:25:35	0:13:50
E5	5000	1:42:35	1:12:29
F5	86000	0:22:35	0:12:58

		Bypass agent	lag phase time [min]	peak height Thrombin [nM]	peak height time [min]	AUC
No170	RDL	Before	62.1	#DIV/0!	0.1	0.0
No171	RDL	After	9.1	100.8	28.6	2976.4
No170	RDH	Before	63.6	#DIV/0!	0.1	0.0
No171	RDH	After	9.6	93.3	23.1	2223.9

Graph3 treatment by rFVIIa



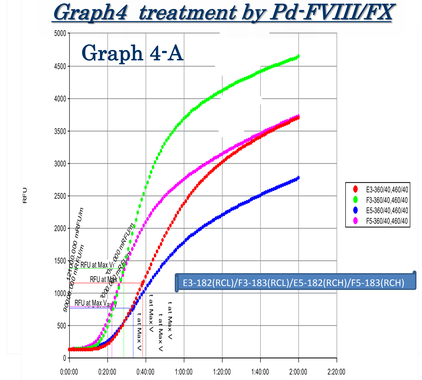


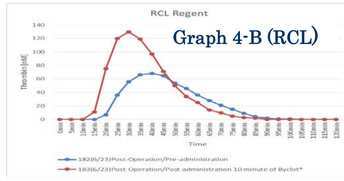


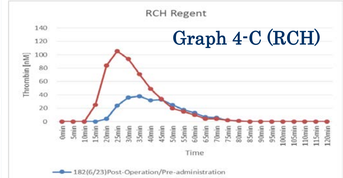
Well	Max V [360/40,460/40]	t at Max V [360/40,460/40]	Lagtime [360/40,460/40]
C3	85000	0:38:35	0:24:39
D3	90000	0:32:35	0:19:44
C5	46000	0:31:35	0:18:47
D5	72000	0:28:35	0:18:41

		Bypass agent	lag phase time [min]	peak height Thrombin [nM]	peak height time [min]	AUC
No180	RDL	Before	18.1	85.6	38.6	2944.1
No181	RDL	After	15.6	104.5	31.6	3321.2
No180	RDH	Before	15.1	39.1	32.1	966.2
No181	RDH	After	13.6	73.2	27.6	1888.6

Graph4 treatment by Pd-FVIII/FX







Well	Max V [360/40,460/40]	t at Max V [360/40,460/40]	Lagtime [360/40,460/40]
E3	67000	0:38:35	0:23:18
F3	121000	0:28:35	0:18:17
E5	48000	0:33:35	0:20:13
F5	90000	0:22:35	0:15:13

		Bypass agent	lag phase time [min]	peak height Thrombin [nM]	peak height time [min]	AUC
No182	RDL	Before	17.6	68.9	40.1	2550.4
No183	RDL	After	14.6	131.2	28.6	3822.2
No182	RDH	Before	16.1	39.1	34.1	1203.2
No183	RDH	After	12.1	104.9	24.1	2592.8

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