FACTOR VIIa USED TO STOP BLEEDINGS IN DIFFERENT CONDITIONS ASSOCIATED WITH DIC

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REZUMAT

Factorul VIIa (FVIIa) a apărut ca alternativă terapeutică la pacienţii hemofilici care dezvoltă anticorpi anti F VIII şi/ sau anti F IX.

Mecanismul de acţiune este asigurarea hemostazei la locul injuriei vasculare independent de prezenţa F VIII şi/ sau F IX, prin formarea unui complex cu factorul tisular (FT). Complexul astfel alcătuit are intensă activitate proteolitică şi activează F X la F Xa, ducând la generarea de mici cantităţi de trombină. Cascada coagulării decurge apoi în secvenţă normală.

Articolul prezintă utilizarea F VIIIa în sângerări asociate coagulării intravasculare diseminate (CID) de diverse etiologii, cu hemoragii care nu au putut fi oprite prin terapia convenţională: masa eritrocitară (MER), plasma proaspătă congelată (PPC), concentrat trombocitar (CT), crioprecipitat (nu s-au putut folosi şi estrogeni conjugaţi).

Eficienţa F VIIa (NOVOSEVEN, NOVO NORDISK, A/ S) a fost susţinută de oprirea sângerărilor în toate cele 6 cazuri, cu variaţie diferită a celorlalţi parametri cuantificaţi.

Cuvinte cheie: F VIIa, CID, sângerări diverse.

Recombinant Factor VIIa (NovoSeven®) occurred as a treatment option for patients with hemophilia who developed inhibitors against clotting factors VIII and/or IX. It ensures effective haemostasis at the site of injury, independent of the presence of FVIII and/or FIX, by forming complexes with exposed tissue factor (TF). Tissue Factor is a membrane-bound glycoprotein expressed on cells in the sub-endothelium. It has a high affinity for FVIIa with whom it forms complexes with important proteolytic activity.

The TF: FVIIa complex activates FX to FXa leading to the generation of small amounts of thrombin (IIa). This limited amount of thrombin subsequently activates the co-factors factor V (FV) and FVIII, as well as platelets accumulated at the site of injury. The activated platelets expose phosphatidyl serine on their membrane and provide the template for further thrombin generation.

The expression of abnormal amounts of TF, in pathological conditions like advanced arteriosclerosis, crush injury or septicemia may increase the risk of development of thrombotic events or induce disseminated intra-vascular coagulation (DIC) in association with NovoSeven treatment.

Although the DIC may have different etiologies, the diagnostic criteria include:

- microangiopathic hemolytic anemia
- thrombocytopaenia
- prolongation of PT and APTT

Laboratory references:

Parameters	Normal values
HBG (g/dl)	11 – 16.5
HCT (%)	34 –54
WBC ($x10^3/\mu L$)	4 – 9
PLT ($x10^3/\mu L$)	150 – 350
Urea (mg/dl)	15 – 43
Creatinine (mg/dl)	0.6 – 1.2
ALAT (U/l)	21 – 72
ASAT (U/l)	14 – 50
APTT (sec.)	20 – 30
PT (sec.)	11 – 13
Fibrinogen (mg/dl)	200 – 400
D-dimers (ng/dl)	< 200
Bilirubin Total (mg/dl)	0.2 – 1.3

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- D-dimers
- lowering of plasma fibrinogen
- diffuse bleedings

The actual therapy aims to stop the bleeding by targeting the normalization of the affected parameters through the administration of packed cells, fresh frozen plasma (FFP), platelet concentrates, conjugated estrogens and fibrinogen, depending on the etiology.

We hereby present 6 cases with DIC of diverse etiology, complicated with diffuse bleedings - epistaxis, hematuria, and UGI hemorrhage — in which the abovementioned therapy was not able to stop the bleedings. The administration of rFVIIa (NovoSeven®, Novo Nordisk AIS) in doses of 90 pg/kg b.w. eventually repeated after two hours, led to the cessation of bleedings in all cases.

A possible explanation of NovoSeven's efficiency in these cases could be the additional thrombin generation on the surface of activated platelets. The thrombin excess may also restore the normal resistance against fibrinolysis through the activation of the "Thrombin Activatible Fibrinolytic Inhibitor" (TAFI).

rFVIIa induces haemostasis at the site of injury, and published evidences have mentioned only laboratory signs indicative of potential systemic activation of the coagulation during NovoSeven® therapy. Nevertheless, further controlled, prospective studies are necessary in order to rule out the relative contraindication of NovoSeven®Is administration in DIC.

Case No. 1: Clinical data

1.	**Patient's initials:**	O. I.
2.	**Age:**	29
3.	**Gender:**	F
4.	**Diagnostic at admission:**	Multiple systems/organs failures post-abortum. Acute renal failure (ARF). Acute hepatic failure (AHF). Acute respiratory distress syndrome (ARDS). Disseminated intra-vascular coagulation (DIC).
5.	**Bleeding type:**	Massive bleeding through surgical wound Arround draining tubes and dialysis catheter
6.	**Therapy before NovoSeven® administration:**	Replacement therapy with: Fresh Frozen Plasma 10 U Packed cells 6 U Platelet concentrate 18 U Cryoprecipitate 2 U
7.	**Haemodialysis:**	2 sessions before, and 9 sessions after NovoSeven® administration
8.	**NovoSeven® administration:**	1 dose of 90 µg/kg b.w. on day 5

Comments:

- after NovoSeven® administration, the evolution of coagulation parameters and platelets number could not be correlated with the cessation of bleedings.
- although D-dimers maximum values were observed during the first one or two days following NovoSeven® administration, they diminished progresively afterwards.
- death occurred on the 20th day of hospitalization due to multiple systems/organs failures.

Case No. 1: Laboratory assessments during hospitalization

	Hospitalization Days (N7)																			
Laboratory parameters	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20
HBG (g/dl)	6.6	7.3	9	10.2	7.2	7.9	6.8	7.2	7.5	7.8	7.3	6.4	6.6	6.3	6.4	6.8	6.6	7.1	6.8	8.1
HCT (%)	18.9	21.1	27.2	30.7	21.5	24.6	20.1	22.5	23.2	24.2	23.9	19.8	19.5	19.2	19.4	19.8	19.6	22.4	21.9	25.9
WBC ($x10^3/\mu L$)	32.8	42.5	48.6	52.1	47.4	58.5	40	28.5	21	11	15.9	20	17.1	20	16.5	19.2	22.4	11.3	21.3	19.9
PLT ($x10^3/\mu L$)	21	25	40	35	25	37	40	89	167	229	195	201	109	108	121	136	177	180	120	113
Urea (mg/dl)	127	116	139	126	184	172	226	176	165	186	136	175	189	180	177	250	235	166	181	256
Creatinine (mg/dl)	5.1	4.1	5.6	4.9	6	5.4	6.7	5	4.6	4.5	2.8	4.1	3.9	4.7	-	-	6.4	3.7	3.5	6.8
ALT (U/l)	197	98	78	72	-	-	19	17	-	-	45	-	-	25	-	-	45	-	139	-
AST (U/l)	439	182	155	136	-	-	37	34	-	-	88	-	-	41	-	-	40	-	184	-
APTT (sec.)	49.9	97.2	72.5	44.1	42.5	47	18.6	87.6	-	-	17.4	19.6	23.3	16.2	-	-	-	-	97.4	-
PT (sec.)	16.6	-	13.4	17.4	18.1	14.3	14.9	12.5	15	-	-	13.2	-	13	-	-	-	-	15.3	-
Fibrinogen (mg/dl)	366	-	-	240	200	-	-	360	-	-	499	-	-	499	-	-	483	-	525	-
D-dimers (ng/dl)	400	600	600	1600	2400	2400	-	1400	-	-	800	-	-	600	-	600	400	-	400	-
Bilirubin Total (mg/dl)	7.8	-	4.3	3.4	2.7	2.1	1.7	1.5	-	-	5.5	5.9	-	-	7.6	-	3.1	-	14.7	-

Case No. 2: Clinical data

1.	**Patient's initials:**	I. I.
2.	**Age:**	51
3.	**Gender:**	M
4.	**Diagnostic at admission:**	Resuscitated cardiopulmonary arrest Leptospirosis Acute Renal Failure (ARF) Acute hepatic failure Disseminated intra-vascular coagulation (DIC)
5.	**Bleeding type:**	Melena Haematemesis Bleeding through the catheter Epistaxis
6.	**Therapy before NovoSeven® administration:**	Replacement therapy with: Packed cells 1 U Fresh frozen plasma 16 U Platelet concentrate 6 U Cryoprecipitate 1U
7.	**Haemodialysis:**	1 session before and 5 sessions after NovoSeven® administration
8.	**NovoSeven® administration:**	1 dose of 90 µg/b.w. on day 3

Comments:

- after NovoSeven® administration a progressive increase in platelets number and normalization of coagulation parameters was observed
- the patient was discharged from the ICU on the 11th day

Case No. 2: Laboratory assessments during hospitalization

	Hospitalization Days (N7)										
Laboratory parameters	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**
HBG (g/dl)	11	8.6	7.5	8	7.7	8.4	8.6	7.1	8.5	8.2	7.4
HCT (%)	32	25.8	21.3	23.6	24.3	25.1	26.3	21.6	23.5	23.6	22
WBC ($x10^3/\mu L$)	15.6	19	24	24.5	17.6	19.4	20	17.3	21.7	13.4	10.9
PLT ($x10^3/\mu L$)	24	22	33	74	56	108	105	100	88	85	154
Urea (mg/dl)	275	260	300	261	232	216	217	190	166	223	167
Creatinine (mg/dl)	6.9	4.3	6.7	4.8	5	4.6	5	3.9	3.8	5	4.1
ALT (U/l)	257	132	140	115	108	105	94	66	83	69	54
AST (U/l)	523	282	193	151	140	128	100	87	69	58	41
APTT (sec.)	-	28	44.6	38.3	35	25.7	25.8	-	-	-	-
PT (sec.)	-	14.5	17.5	15.3	13.3	-	-	-	-	10.7	10.6
Fibrinogen (mg/dl)	499	-	210	-	250	-	-	-	-	-	333
D-dimers (ng/dl)	<200	450	1400	1000	800	-	-	650	300	-	<200
Bilirubin Total (mg/dl)	43.5	30	41	42.6	42	43.7	39.8	42	-	-	28

Case No.3: Clinical data

1.	Patient's initials:	T. C.
2.	Age:	28
3.	Gender:	F
4.	Diagnostic at admission:	Chronic glomerulonephritis Chronic renal insufficiency, uremic stage Severe secondary anemia Chronic haemodialysis Disseminated intra-vascular coagulation
5.	Bleeding type:	Massive haemoptysis (origin was not detectable by fiber-optics) Hemorrhagic pleurisy Arround central venous catheter Right thigh haematoma
6.	Therapy before NovoSeven® administration:	Replacement therapy with: Fresh frozen plasma 6 U Packed cells 8 U
7.	Haemodialysis:	According to patient's schedule, initially without heparin
8.	NovoSeven® administration:	2 doses of rFVIIa, 90 µg/kg b.w. each, in day 3 and day 8[1]

Comments:

- the evolution of coagulation parameters could not be correlated with the cessation of bleedings after NovoSeven® adminisration

Spectacular clinical improvement after NovoSeven® administration

Case No. 3: Laboratory assessments during hospitalization

	Hospitalization Days										
			↱ N7					↱ N7			
Laboratory parameters	1	2	3	4	5	6	7	8	9	10	11
HBG (g/dl)	5.6	5.5	5.1	7.6	8	7.7	9.4	6.8	8.4	8.5	8.6
HCT (%)	18.2	16.9	15.8	23.4	24	22.8	28.8	20.9	25.6	25.5	25.4
WBC ($x10^3/\mu L$)	12.2	7.9	9.9	8.3	11.5	10.4	5.5	8.3	8.3	9	8.8
PLT ($x10^3/\mu L$)	138	139	109	110	148	160	102	168	90	135	231
Urea (mg/dl)	259	167	140	92	101	155	66	112	138	87	94
Creatinine (mg/dl)	11.1	7.3	5.5	6.7	7.2	4.9	5	5.8	4.6	5.1	2.9
ALT (U/l)	37	31	-	-	-	-	-	-	-	-	26
AST (U/l)	26	18	-	-	-	-	-	-	-	-	19
APTT (sec.)	21.2	21.5	55.3	31.8	26.2	27.5	23.2	50.1	38.3	36.2	28
PT (sec.)	12.9	14.3	18.3	16.2	14.1	13.2	11.1	16.3	15.8	15.7	13
Fibrinogen (mg/dl)	152	199	190	247	390	280	260	182	210	350	360
D-dimers (ng/dl)	400	800	1800	1600	1400	800	900	1800	1400	600	400
Bilirubin Total (mg/dl)	1	1.8	1.8	1.3	1	-	-	-	-	-	-

Case No. 4: Clinical data

1.	Patient's initials:	S. P.
2.	Age:	29
3.	Gender:	F
4.	Diagnostic at admission:	Primary purulent peritonitis Mesenteric adenopathy Acute Renal Failure (ARF) Disseminated intra-vascular coagulation (DIC)
5.	Bleeding type:	Massive bleeding through surgical wound Arround dialysis catheter
6.	Therapy before NovoSeven® administration:	Replacement therapy with: Fresh frozen plasma 11 U Packed cells 3 U
7.	Haemodialysis	1 session before and 4 sessions after NovoSeven® administration
8.	NovoSeven® administration:	2 doses of 90 µg/kg b. w. of rFVIIa, at two hours interval, on day 3

Comments:

- progressive normalization of coagulation parameters after NovoSeven® administration

Case No. 4: Laboratory assessments during hospitalization

	Hospitalization Days											
			2xN7									
Laboratory parameters	1	2	3	4	5	6	7	8	9	10	11	12
HBG (g/dl)	10.7	8.3	6.9	7.9	-	9.9	10.3	8.4	8.8	9.1	9.6	9.4
HCT (%)	29.9	23.9	18.8	21.8	-	28.4	29.2	24.4	26	27.5	28.3	28
WBC ($x10^3/\mu L$)	13.4	15.5	14.5	13.3	-	26.3	19.4	15.9	13.8	9.1	6.4	7
PLT ($x10^3/\mu L$)	234	229	105	176	-	281	293	299	305	319	338	330
Urea (mg/dl)	139	154	115	117	-	124	108	100	50.6	35	30	32
Creatinine (mg/dl)	11.1	12.2	9.5	10.1	-	10.6	8	6.1	4.3	3.1	2	1.3
ALAT (U/l)	31	38	33	-	-	121	127	85	56	-	57	50
ASAT (U/l)	22	37	26	-	-	168	108	76	29	-	49	30
APTT (sec.)	30.5	33.1	45.6	40.3	-	36.9	28.5	23.3	26.2	-	29.3	27.6
PT (sec.)	13.1	14.4	17.5	16.4	-	14.1	14.5	12.9	13.7	-	12.7	12.5
Fibrinogen (mg/dl)	366	240	190	200	-	390	403	355	531	-	449	345
D-dimers (ng/dl)	<200	360	900	1000	800	600	600	400	200	<200	<200	-
Bilirubin Total (mg/dl)	2.4	2.6	2.3	-	-	-	-	-	-	-	1.3	-

Case No. 5: Clinical data

1.	**Patient's initials:**	T. M.
2.	**Age:**	31
3.	**Gender:**	F
4.	**Diagnostic at admission:**	Hemolytic uremic syndrome of unknown etiology Acute Renal Failure (ARF) in functional recovery stage Recent partial meniscectomy Disseminated intra-vascular coagulation (DIC)
5.	**Bleeding type:**	At the venous puncture sites
6.	**Therapy before NovoSeven® administration:**	Replacement therapy with: Fresh frozen plasma 4 U limited Platelet concentrate 3 U supply was Packed cells 2 U available
7.	**NovoSeven® administration:**	2 doses of rFVIIa 90 µg/kg b. w. at two hours interval, on the first day
8.	**Haemodialysis**	6 sessions. The insertion of the dialysis catheter was performed after NovoSeven® administration (see also E Moisescu, I Simion, A Mureşan, R Ciupan "Recombinant factor VIIa treatment of bleeding associated with acute renal failure". *Blood Coagulation & Fibrinolysis*; September 2000;11:575-577.)

Comments:

- increase in D-dimers plasma concentration after NovoSeven® administration, followed by progressive normalization
- NovoSeven® administration led to cessation of bleedings

Case No. 5: Laboratory assessments during hospitalization

	Hospitalization Days (2xN7)								
Laboratory parameters	1	2	3	4	5	6	7	8	9
HBG (g/dl)	7.3	7.5	7.9	8.1	8.4	8.5	8.4	7.5	7.7
HCT (%)	21.6	22.5	23	25.1	23.8	24	23.5	21	22.9
WBC ($x10^3/\mu L$)	3	3.2	7.8	14.2	13	16	15	11.4	6.5
PLT ($x10^3/\mu L$)	39	40	50	45	52	56	74	105	115
Urea (mg/dl)	153.3	131.7	193.3	175.3	173.2	132	129	209	147
Creatinine (mg/dl)	5	4.5	6.6	5.6	4.3	4.2	3.8	6.1	4.3
ALAT (U/l)	109	86	63	58	45	42	40	-	-
ASAT (U/l)	274	120	126	50	43	62	56	-	-
APTT (sec.)	45.1	35.2	33	31.1	26.1	-	27.4	25.4	25.9
PT (sec.)	16.7	14.1	13.6	12.2	12.1	-	13.2	12.4	13
Fibrinogen (mg/dl)	160	184	210	247	336	-	311	266	246
D-dimers (ng/dl)	1600	1400	1200	1000	600	-	400	300	<200
Bilirubin Total (mg/dl)	3.5	1.9	1.1	0.8	1.8	-	0.5	0.7	0.5

Case No. 6: Clinical data

1.	**Patient's initials:**	M. M.
2.	**Age:**	73
3.	**Gender:**	M
4.	**Diagnostic at admission:**	Acute Renal Failure – diuresis recovery stage after cholecystectomy Essential hypertension, stage II Disseminated intra-vascular coagulation (DIC)
5.	**Bleeding type:**	Through surgical wound Arround central venous and dialysis catheter At the venous puncture sites
6.	**Therapy before NovoSeven® administration:**	Replacement therapy with: Fresh frozen plasma 4 U Packed cells 4 U
7.	**Haemodialysis:**	1 session, without heparin on the first day
8.	**NovoSeven® administration:**	1 dose of rFVIIa, 90 µg/kg b.w. on day 2

Comments:

- cessation of bleeding 3 hours after NovoSeven® administration

Case No. 6: Laboratory assessments during hospitalization

	Hospitalization Days											
		N7										
Laboratory parameters	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**
HBG (g/dl)	10.6	5.7	5.6	7	8.5	8.7	-	7.5	6.4	7.2	7.7	7.5
HCT (%)	32.5	18.5	17.6	21.9	26.1	27.6	-	20.7	17.9	20.2	23.8	22.9
WBC ($x10^3/\mu L$)	13.2	16.7	16.3	16	16.7	17.9	-	15.3	16	17.3	11.8	11.4
PLT ($x10^3/\mu L$)	352	40	85	170	164	148	-	153	95	85	85	96
Urea (mg/dl)	162.3	120	185	194	153	133	-	104	138	167	130	105
Creatinine (mg/dl)	7.4	5.7	7.8	7.4	6.3	5.3	-	4.3	6.5	7.9	5	4.1
ALAT (U/l)	110	70	-	-	-	-	-	-	-	-	-	-
ASAT (U/l)	82	57	-	-	-	-	-	-	-	-	-	-
APTT (sec.)	21.2	49.1	42	38	37.5	-	-	32.5	-	-	-	-
PT (sec.)	14.8	23.8	17.7	15.1	14	-	-	14	-	-	-	-
Fibrinogen (mg/dl)	320	170	182	201	230	-	-	250	-	-	-	-
D-dimers (ng/dl)	<200	1600	1400	1400	1000	-	-	800	-	-	-	-
Bilirubin Total (mg/dl)	1	2.5	-	-	-	-	-	1.4	-	-	-	-

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