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Concentration of Thrombin Activatable Fibrinolysis Inhibitor (TAFI) in the Process of Wound Healing After the Neurosurgery: Preliminary Report

KEYWORDS: Thrombin Activatable Fibrinolysis Inhibitor, treatment, wound healing

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ABSTRACT *Background. In the process of post surgical wound healing locally secreted relays are involved, including also pro-angiogenic factors, factors of hemostasia or fibrinolysis. The function of TAFI in this process is not fully elucidated. The main purpose of this study was to estimate the concentration of thrombin activatable fibrinolysis inhibitor in blood serum of the patient with a surgery wound at each measurement before and after the surgery. Methods. The study included 20 adult patients who received a surgical treatment because of degenerative spine changes. The test consisted in three-time determination of TAFI concentration in blood serum of the patients tested. Conclusions. No statistically significant difference in TAFI concentration in blood serum of the tested patients was observed in each measurement before and after the surgery. TAFI concentration in blood serum of the patients operated on differs significantly compared to the control group in measurement one and three.*

Introduction

The wound healing process is a dynamic and multi-stage process consisting in interaction of numerous biologically active molecules. This process consists of four phases: (1) hemostasis-, protection against local bleeding taking place due to platelet aggregation and activation of the coagulation cascade, (2) inflammatory phase – generating neutrophils to inhibit bacterial invasion, (3) differentiation stage, proliferation of mesenchymal cell migration and (4) tissue remodeling, which closely cooperate with each other and occur in adequate turn (Gosain, & Dipietro, 2004; Guo, & Dipietro, 2010; Hoffman at al., 2006; Laurens, Koolwijk, & De Maat, 2006; Nowak, & Olejek, 2004). Leukocytes, fibroblasts and blood vessels move to the repair space and take part in the tissue regeneration process (Laurens, Koolwijk, & De Maat, 2006).

Plasmin as well as other components of the fibrinolytic system actively participate in tissue repair by regulating extracellular matrix remodeling (ECM). Also, TAFI recently discovered protein which is considered to be a link between the clotting process and fibrinolysis, also actively involved in the wound healing process (Boffa, 2003). Decrease of TAFI concentration may lead to impaired wound healing (Hoffman at al., 2006; te Velde at al., 2003).

The analysis of the literature suggests that there are only a few studies regarding thrombin activatable fibrinolysis inhibitor (TAFI) function in the process of wound healing which were mainly carried out on mice.

The main purpose of this study was the assessment of thrombin activatable fibrinolysis inhibitor (TAFI) in blood serum of the patients with post-surgery wound in each measurement before and after surgery. Detailed research problems are presented in the form of questions: Does TAFI concentration in the blood of operated patients significantly differ compared to the control group? Does TAFI concentration in blood significantly differ in the measurements before and after the surgery? Is there a correlation between each measurement in TAFI concentration?

Material and Methods

Patients

The tests were carried out at Neurosurgical Department and Clinic, Collegium Medicum (CM), Nicolaus Copernicus University (NCU) on the group of 20 patients (9 men and 11 women) at the age of 7-54 lat (average 44±8), subject to surgery treatment because of the degenerative change in the spine.

From the studies there were excluded patients who had been diagnosed, apart from the basic unit, another central neural system disease (for example.: proliferative process, vascular malformation as well as diseases with a known impact on the wound healing process, such as accompanying atherosclerosis and its complications, diabetes in pregnancy, cancer, AIDS). Also, there were excluded patients, who had been operated on within the period shorter than 30 days preceding their admission to Neurological and Neurosurgical Nursing Department.

The control group consisted of 20 healthy volunteers selected according to sex and age criteria (to the tested group). To the control group there were qualified healthy people who had not been treated by then.

Methods

The test consisted in three-time venous blood sampling (5 cm of blood) from venipuncture around the bend of the el-

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bow, without venous stasis, using a vacuum blood-collecting system. Blood was collected into polyethylene test-tubes, containing 3,2% of sodium citrate in a ratio of 9:1. The first sampling was made in the period of 24 hours to 1 hour before the surgery commencement (measurement 1). The second sampling was made on the first day after the surgery (measurement 2). The third sampling took place between the 5th and 7th day after the surgery (measurement 3). All measurements were performed in the morning on fasted patients. For the determination of the tested parameters there was always used the patient's blood sampletaken in connection with the necessity to carry out laboratory tests necessary in the diagnostic - therapeutic process during the hospitalization period.

Blood samples from people of the control group were taken in the morning after previous half an hour - relax without venous stasis, using a vacuum blood-collecting system.

Blood was collected, just as in the case of ill patients, into polyethylene test-tubes, containing 3,2% of sodium citrate in a ratio of 9:1and handed over to Hemostatic Disorders Laboratory, Department of Pathophysiology, CM, NCU in Bydgoszcz in order to determine TAFI concentartion by means of ELISA method.

Ethical considerations
For the performance of tests there was obtained the consent from Bioethics Committee of Nicolaus Copernicus University in Toruń.

Statistical analysis
The statistical analysis was performed with Microsoft Excel and STATISTICA version 9.1. The distribution of the analyzed parameters is different from a normal distribution, therefore nonparametric tests were applied in the statistic analysis; Friedman ANOVA to compare the data collected in each measurement). In order to compare the average from the two groups (research and control) Mann-Whitney test was applied (Z). In the assessment of correlations between individual factors (concentrations), Pearson's correlation coefficient (r_p) was applied. The statistical hypotheses were verified at the level of significance $p<0.05$.

Results
Differences in TAFI concentration in blood in the research group and in the control group in each measurement

In measurement one a statistically significant difference between TAFI concentration in the research group and TAFI concentration in control group was found, Mann-Whitney test Z=-2.52; p=0.012. In measurement two, no statistically significant difference was found between TAFI concentration in the research group and TAFI concentration in the control group. In measurement three a statistically significant difference was found between TAFI concentration in the research group and TAFI concentration in control group, Mann-Whitney test Z=-2.48; p=0.013

Table 1. TAFI concentrations in blood of the patients (research group) and healthy people (control group) in consecutive measurements

	Research Group		Control Group		
	Average	SD	Average	SD	p
Measurement 1					
TAFI [ng/ml]	5.572	14.322	32.290	59.473	0.012
Measurement 2					
TAFI [ng/ml]	8.771	18.685	32.290	59.473	0.09
Measurement 3					
TAFI [ng/ml]	3.617	9.835	32.290	59.473	0.013

SD, standard deviation; TAFI, fibrinolysis inhibitor activated by thrombin

Dynamics of changes in TAFI concentration in the research group at each measurement

No statistically significant difference in TAFI concentration between each measurement before and after the surgery was found, χ^2ANOVA(n=20,df=2)=1.63; p=0.44 (n.s.)

Table 2. TAFI concentration in blood serum in each measurement

	Descriptive statistics	Measurement			p
		1	2	3	
TAFI [ng/ml]	Min	0.00	0.00	0.00	0.44
	Max	57.260	75.230	42.560	
	Me	0.00	0.00	0.00	
	Mean	5.572	8.771	3.617	
	SD	14.322	18.685	9.835	

Min-minimum value, Max-maximum value, Me-median value, SD-standard deviation

Correlation between each TAFI concentration measurement
There was no statistically significant correlation between the TAFI level before the surgery (measurement 1) in the research group and the TAFI level just after the surgery (measurement 2), r_p=0.13; p=0.59 (n.s.) as well as in measurement 3, r_p=0.14; p=0.57 (n.s.). There was also no statistically significant correlation between the TAFI level just after the surgery (measurement 2) in the case of persons in the research group and the TAFI level after the surgery in measurement 3, r_p=0.32; p=0.16 (n.s.)

Table 3. Correlation between TAFI concentration in each measurement (*p*)

TAFI			
	First TAFI	Second TAFI	Third TAFI
First TAFI	-	0.59	0.57
Second TAFI	0.59	-	0.16
Third TAFI	0.57	0.16	-

Discussion
In the current study, in measurement one and three there was obtained considerably lower TAFI concentration in the group of patients who underwent surgery due to degenerative changes of the spine, compared to persons from the control group.

TAFI participates in the wound healing process by means of its antifibrinolytic and anti-inflammatory properties. Decreased TAFI concentration results in the impairment and in delay of the wound healing process (Verkleij at al., 2010). Additionally, lower TAFI concentration was observed in the case of patients suffering from acute myelogenous leukemia (Sokołowski, Galar, & Kłoczko, 2006). A very low TAFI concentration is observed in the case of patients suffering from cirrhosis of the liver, and virtually no detectable levels are recorded in the case of liver cancer (Nesheim, 2003). Pathological decrease in TAFI activity, may increase the tendency to bleed which might be related to the impaired tissue repairs in these patients. Whereas exceeded TAFI activation may lead to a tendency to clot (Boffa, 2003). Watanabe and partners observed lower TAFI concentration in DIC which might be related to the consumption of this inhibitor. They also obtained a negative correlation between TAFI antigen and activity and fibrinogen level, PAP complexes as well as t-PA/PAI-1, the authors think that TAFI plays an important role in the DIC pathogenesis (Watanabe, at al., 2001). Besides, in the context of our studies it is quite interesting that there is a the positive correlation between TAFI concentration and women's age whereas a similar correlation was not observed with men (Chetaille, at al., 2000).

te Velde and partners speculate, that the active TAFI inhibits

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the activation of plasmin, however, in a situation of TAFI deficiency there may take place an uncontrolled generating of plasmin and as a consequence to an incorrect degradation of the extracellular matrix leading to excessive removal of fibrin and to pathological effect on keratinocytes migration (te Velde at al., 2003).

Conclusions

1. There was no statistically significant difference in TAFI concentration in blood serum of the persons tested at each measurement before and after the surgery.
2. TAFI concentration in blood serum of the persons operated on differs significantly when compared with the control group in measurement one and three.
3. There was no statistically significant correlation between TAFI concentration in each measurement.

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