

Correlation of Blood Fibrinolytic Activity and Clinical Outcome After Oral Surgery Interventions

SUMMARY

The primary aim was to investigate how the oral surgical interventions, as psychophysical and operative trauma, influence the response of the blood fibrinolytic system, and whether the possible changes in the level of the activators and inhibitors of the fibrinolytic system could correlate to clinical results. Fourthly healthy subjects with operative tooth extractions were included in the research; 35 subjects, blood donors, constituted a control group. The influence of the interventions over the parameters of the blood fibrinolytic system was examined prior to surgery and immediately after the extraction with Elisa test. The values of the blood pressure and pulse frequency prior to the surgery; after the applying of the local anaesthesia and immediately after the performed interventions were the only objective parameters for the evident physical reflections of the stress. At the control investigations, after 24, 48, hours and seven days, certain changes like oedema, haematoma, pain and dry socket have been presented.

Decreased values of t-Pa and PAI-1 after the oral surgery were found at a high statistically significant difference. The analysis of diastolic blood pressure and pulse frequency values showed statistic significance, showing psychological dimension of oral surgery. There was a positive correlation between most of the parameters from the control examinations and the parameters (t-Pa, PAI-1, pro-activators and inhibitors) of the fibrinolytic system in the examined group.

Oral surgical intervention, as a stress factor, had influence and affects the fibrinolytic process through the effect upon pro-activators and inhibitors of the fibrinolytic system, and severity of the clinical outcome after tooth extraction. Parameters of fibrinolytic system, t-PA and PAI-1, can be the most sensitive markers of reaction to oral surgical stress.

Keywords: Tooth Extraction; Oral Surgery; Fibrinolytic System; Stress

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Introduction

Many authors^{4-8,27} set an aim to evaluate the influence of the surgery stress and the operative trauma over certain parameters of coagulation and blood fibrinolysis.

According to Grand⁸, the acute physical stress as the major surgery is, the insulin induced hypoglycaemia and the physical exercises are connected to acute increase of concentration of the factor VIII in circulation, as well as increased blood fibrinolytic activity. The mechanisms that are included in the production of these answers are partly

under hormone control and it is obvious that the changes are mediated by the neuro-hormones adrenalin and arginine-vasopressin.

Kehlet¹³ emphasized that surgery trauma and modified effects of pain are the reason for start of possible complications, as infection and the haemorrhage are. Exactly, as a consequence of the activation of humoral substances (prostaglandin, kinin, leukotriene, interleukin-1, as well as the tumour necrotizing factor), the creation of mentioned complications is possible². The interleukin-1, as a mediator of an inflammatory reaction, and the tumour necrotizing factor lead to pro-coagulation

changes in the one-body cells. Here are the synthesis and secretion of the thromboplastin, antigen activity of F VIII: factor von Willebrand, then activity of the inhibitor of the plasminogen-1 (PAI-1) activator with the decreased production and secretion of the tissue type plasminogen activator (t-PA) at same time.

In contemporary scientific books^{1,2,17} there is an elaboration of accidentally discovered cases with prolonged bleeding after tooth extraction¹⁸ in patients with rare deficits of some factors of coagulation^{17,18,23} or inhibitors of fibrinolysis^{11,12,14,15,20,25,26}.

The basic aim of this research was to determine whether the oral surgical interventions as psycho-physic and operating trauma influence the answer of blood fibrinolytic system. The second aim was to determine the correlation of values of the level of fibrinolytic system activators and inhibitors, and clinical outcome after oral surgery.

Material and Methods

These researches covered 40 healthy patients of both sex, 25-35 years of age. According to the history data, clinical and radiographic examination, indications for operative extraction were set up (roots with different chronic lesions in the molars region). The surgical interventions were done for 35-40 min, and the operative trauma was similar in the examinees according to the operative protocol. The interventions in the examined group were realized during the morning hours at the Clinic for Oral Surgery, University Dental Clinical Centre "St Panteleimon" in Skopje. The control group consisted of 35 healthy examinees of both sex, blood donors, 25-30 years of age, who didn't have any dental intervention. All examinees agreed to be included in our research.

Venous blood samples were taken before and after surgery from the examined group and also, from the control group. The blood samples were instantly distributed to the Institute of Blood Transfusion, Department for Haemostasis and Thrombosis, at the Medical Faculty in Skopje. There was a selective determination of the plasminogen activator - tissue-type plasminogen activator (t-PA antigen - t-PA-Ag) - INNOTEST t-PA, and of the inhibitors of plasminogen activator-antigen (Plasminogen activator inhibitor-1-antigen; PAI-1-Ag), with INNOTEST PAI-1 (Biopol Trinity Company, Ireland). Bought tests are immuno-enzymatic analysis - MIKRO-ELISSA method, with double antibody or sandwich method where the antigen is inserted.

As objective parameters of the physical reflection of stress the values of blood pressure and pulse rate were recorded in 4 phases: before surgery, after the application of local anaesthesia, during surgery, and at

the end of it. Presence of fear according to the subjective statements was recorded in all the examinees. The control investigations were done 24, 48 hours and 7 days after surgery, recording the presence of oedema, haematoma, pain, dry socket and prolonged bleeding.

For statistics elaboration and analysis of the obtained data, the statistics programme "Statistica" was used.

Results

The distribution of the values for t-PA and PAI-1 for the examined group, before and after surgery, is showed in figure 1. The value of t-PA after the surgical extractions (3.55 ng/ml) is lower comparing to the value before them (4.43 ng/ml), showing statistically significant difference ($t = 3.29$; $p < 0.01$). The value of PAI-1 after surgical extractions (56.3 ng/ml) is significantly lower comparing to the average value of PAI-1 before surgery (71 ng/ml). Their analysis showed statistically significant difference ($t = 2.59$; $p < 0.05$).

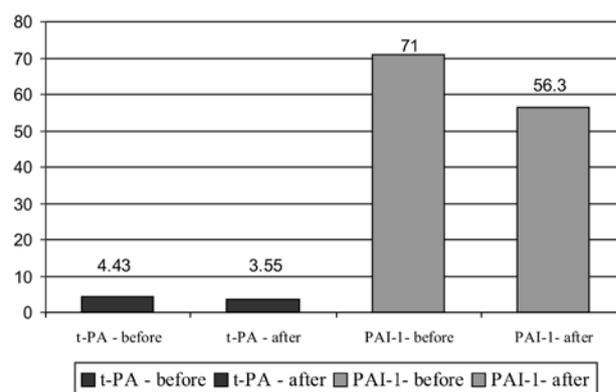


Figure 1. Values of t-PA and PAI-1 before and after oral surgery

The values of t-PA and PAI-1 before and after surgery in the examined group were significantly higher comparing to the same parameters at the control group, and the analysis of average values showed statistically significant difference in all of the examined relations (t-PA contr./t-PA before: $t=4.26$, $p<0.01$; t-PA contr./t-PA after: $t=2.21$, $p<0.05$; PAI-1 contr./PAI-1 before: $t=7.89$, $p<0.01$; PAI-1 contr./PAI-1 after: $t=6.60$, $p<0.01$), which is shown in figure 2.

Average values of systole and diastole blood pressure at the examined group are shown on figure 3. The analysis of average values of systole pressure between the examined and the control group in all of the researching phases did not show statistical difference. The analysis of average values of the diastolic pressure between the examined and the control group in all of the researching

phases did not show statistical difference except in the relation before surgery/ after anaesthesia ($t = 2.76$, $p < 0.001$).

The average values of the pulse rate at the examined group are shown in figure 4. The analysis of average values between the examined and the control group showed high statistical difference in relation control pulse rate/pulse rate before surgery ($t = 4.33$, $p < 0.001$). In the rest of the researched relations, there was no significant difference ($t = 0.33$; 0.87 ; 0.95 and $p < 0.05$).

Subjective statements for the presence of fear among the examinees with extractions are shown in table 1. Before the extraction, 13 of the examinees (32.5%) had no

fear, while 27 (67.5%) felt fear; 22 examinees (55%) felt fear during the intervention.

After 24 and 48 hours from the extraction, no prolonged bleeding was seen among the examinees. The data for the appearance oedema, haematoma, pain, dry socket in the examined group during the control investigations after 24, 48 hours and 7 days are shown in table 2.

With the Spearman coefficient of correlation (Tab. 3), modest connection was noted between the values of t-PA and PAI-1 after oral surgery and parameters from the control examinations - a domination of values of the relation of PAI-1 after/oedema 24 hours; PAI-1 after/oedema 48 hours; PAI-1 after/dry socket 7 days; t-PA after/dry socket 7 days.

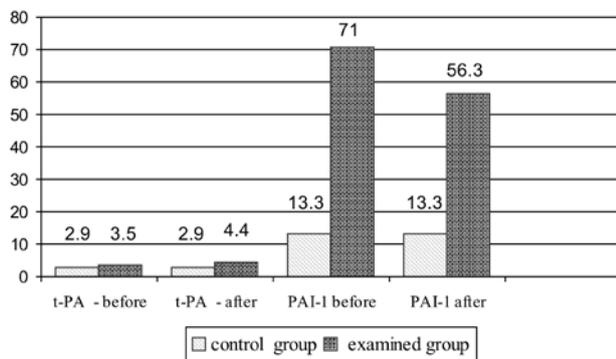


Figure 2. Values of t-PA and PAI-1 before and after oral surgery in the examined and control group

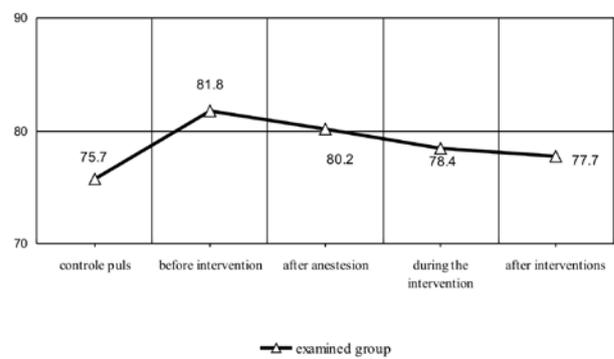


Figure 4. Values of the pulse rate in the examined group

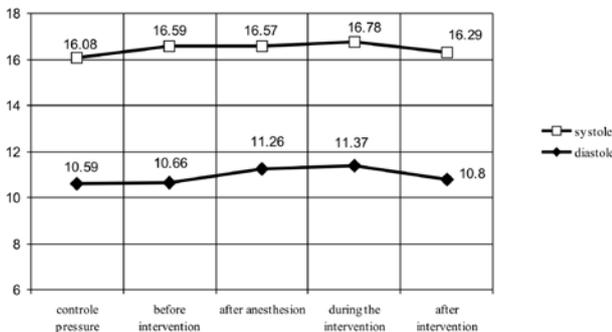


Figure 3. Values of systolic and diastolic blood pressure in the examined group

Table 1. Presence of fear before and after surgery in the examined group

fear	n = 40			
	Before surgery	%	During surgery	%
absence	13	32.5	18	45
presence	27	67.5	22	55
a little	12	30	9	22.5
a few	7	17.5	9	22.5
a lot	8	20	1	2.5
increasing	0	0	3	7.5
differences	Chi Sqr.=1.74			

Table 2. Presence of oedema, haematoma, pain and dry socket after surgery in the examined group

(n = 40)	24 hours				48 hours				7 day			
	oedema		haematoma		oedema		haematoma		oedema		haematoma	
	N ⁰	%	N ⁰	%	N ⁰	%	N ⁰	%	N ⁰	%	N ⁰	%
absence	19	47.5	40	100	30	75	40	100	40	100	40	100
presence	21	52.5	0	0	10	25	0	0	0	0	0	0
	pain		dry socket		pain		dry socket		pain		dry socket	
	N ⁰	%	N ⁰	%	N ⁰	%	N ⁰	%	N ⁰	%	N ⁰	%
absence	17	42.5	40	100	22	55	30	75	40	100	35	87.5
presence	23	57.5	0	0	18	45	10	25	0	0	5	12.5

Table 3. Spearman coefficient of correlation between t-PA and PAI-1 after the interventions and the parameters of the control examinations in the examined group

parameters	Spearman R.	p
t-PA after surgery/oedema 24 h.	- 0.049	p = 0.76
t-PA after surgery/oedema 48 h.	0.043	p = 0.79
t-PA after surgery/oedema 7 days	/	/
t-PA after surgery/haematoma 24 h.	/	/
t-PA after surgery/haematoma 48 h.	/	/
t-PA after surgery/haematoma 7 days	/	/
t-PA after surgery/dry socket. 24 h.	/	/
t-PA after surgery/dry socket 48 h.	0.005	p = 0.97
t-PA after surgery/dry socket 7 days	0.101	p = 0.53
PAI-1 after surgery/oedema 24 h.	- 0.357	p = 0.02
PAI-1 after surgery/oedema 48 h.	- 0.233	p = 0.14
PAI-1 after surgery/oedema 7days	/	/
PAI-1 after surgery/haematoma 24 h.	/	/
PAI-1 after surgery/haematoma 48 h.	/	/
PAI-1 after surgery/haematoma 7 days	/	/
PAI-1 after surgery/dry socket 24 h.	/	/
PAI-1 after surgery/dry socket 8 h.	- 0.32	p = 0.04
PAI-1 after surgery/dry socket 7 days	- 0.167	p = 0.30

Discussion

In our research there is an attempt to give an answer to the question whether minor oral surgery under local anaesthesia in patients with intact system of haemostasis can cause changes to some parameters of the fibrinolytic system. Having in mind complexity of the haemostatic system, we meant to obtain a real clinical evaluation of the physiological activity of blood fibrinolytic system during surgical extractions.

Knowledge about the local haemostatic balance is significantly enlarged with the examination of patients with congenital and acquired defects of coagulation^{11,14,15,20}. In that respect, knowledge of the specific type and strength of the prolonged bleeding is crucial for planning of a safe and suitable oral surgical treatment, with aim to minimize the risk of prolonged bleeding³.

It is stated that the circulation at individuals that are not under stress, t-PA circulates as a complex with PAI-1¹. It is indicative that normally, in the plasma, the bigger part or the whole t-PA is present in the complex with PAI-1. Stimulation like physical activity leads to the release of t-PA, which freely circulates and temporarily stops the PAI-1 effect. The stress, pain, physical exercises, adrenaline injecting or venous occlusion have been known as conditions that

result in significant increase of the plasminogen activators' level^{19,24,27}. Sprengers and Kluft²⁴ reported identical results.

The activation of plasminogen with t-PA is strengthened by the fibrin that creates matrix. In that mean, t-PA and the plasminogen are in suitable position including the conformation changes that make the activation suitable. During the resolution of the fibrin, the connection of the plasminogen and t-PA with the partly degraded fibrin is strengthened, enabling highly efficient fibrinolysis against the decreased concentrations of the involved components. At the same time, t-PA appears in complex with the C-inhibitor and α_2 -MG^{3,6,17}.

Congenital plasminogen activator inhibitor-1 (PAI-1) deficiency is an extremely rare disorder characterized by a bleeding diathesis due to hyper-fibrinolysis as a result of the decreased PAI-1 activity^{11,14,15,25,26}. Takahashi et al²⁵ and Tanimura et al²⁶ presented cases with partial quantitative deficit of the PAI-1 of the members of several families in Japan, that had prolonged bleeding episodes after trauma and tooth extraction. The characteristic disorders of the fibrinolysis with them were: shortened euglobulin lysis time, low level of PAI-1 activity with low levels of the PAI-1 antigens in the plasma and serum. For these patients 5% tranexemic acid as a solution for mouth washing was used in order to decrease bleeding during and after tooth extraction.

The results from our statistical analysis undoubtedly showed that during the surgical extraction in the examined group there were changes of the values of the researched parameters from fibrinolytic system, however without enormously difference; they were in the frames of physiological, referent limits.

Kaličanin and Lečić-Toševski¹⁰ emphasize the Selye's concept: stress reaction is always the same i.e. stereotypical, no matter the kind of stress. Every phase of stress is accompanied by biological modifications and rather stereotypical and characteristic clinical manifestations caused by oscillations of the regulatory biological mechanisms.

However, comprehensive researches^{16,19,21} showed that stress reaction cannot be described as stereotypical changes and processes. Most of the authors^{16,19} agree that psychological, biological and social nature of humans are unique and undivided. So stress, in a best and most correct way, can be defined as a whole psycho-socio-biological answer of the organism towards the action of any agent that attacks its homeostasis.

Raikkonen et al²⁰ researched the effect of chronic stress, comparing to the t-PA and PAI-1 at 69 healthy men. The findings confirm the hypothesis that the chronic stress creates changes in the fibrinolytic system and suggest that the fatness, level of the insulin and triglycerides are in a very close correlation to the fibrinolytic parameters, in other words the increased synthesis of t-PA and PAI-1.

The measurements of blood pressure and pulse rate in this research did not show any bigger differences. Before surgery, after local anaesthesia, during and at the end of surgery, statistically significant differences were

not recorded; while the average values of the diastolic pressure and pulse rate showed statistically significant difference in certain analyzed relations.

Dimova³ emphasized that stress is more present at the examinees with tooth extraction in the examinees with oral surgery. This is confirmed also subjectively with the personal statements of the examinees and objectively through the values of the diastolic pressure and pulse rate. These findings justify pre-surgical psychological treatment of the examinees before oral surgery, which helps in decreasing stress before and during surgery.

Our findings for the presence of oedema and haematoma in the period after the surgery show that there was a moderate correlation with the values of t-PA and PAI-1. In the period after the extraction, no haemorrhage was noticed, which was confirmed at the control examinations. This finding is normal as the examinees were with the intact haemostatic system.

Conclusions

The examinations from this study precisely determined fibrinolytic blood activity during oral surgery and emphasize following conclusions:

Operative extractions had influence on the fibrinolysis by releasing the pro-activators and inhibitors of the fibrinolytic system.

Immuno-enzymatic test of the fibrinolytic activity showed increased values of t-PA before surgery comparing to values of the control group, and some decrease after surgery; these values are in correlation with the increased values of PAI-1.

The values of the examined vital parameters, the blood pressure and pulse rate, as well as data for presence of stress before and during surgery, made a clear view for stress reaction of the examinees. The changes of the values of the diastolic blood pressure and the pulse rate confirm psychological dimension of surgery.

Correlations of the fibrinolytic system parameters with the control examinations parameters (oedema, haematoma, pain and dry socket) showed that there were correlation between the values of t-PA and PAI-1 after surgery, which implicate the clinical outcome of oral surgery. Parameters of the fibrinolytic system, t-Pa and PAI-1, can be used as the most sensitive markers of reaction to surgical stress.

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