

Evaluation of the homeostasis system before and after tooth extraction in patients with viral hepatitis

O.U.Rakhmatullaeva, K.E. Shomurodov, M.M.Fozilov, I.A.Eshmamatov,
Sh.Sh Ikramov.

Tashkent State Dental Institute

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Abstract: The purpose of this study was to assess the state of hemostatic homeostasis in the postoperative period after tooth extraction in patients with viral hepatitis. 58 patients with chronic viral hepatitis were examined. The indicators of the hemostasis system before and after the tooth extraction operation were studied. It was revealed that the indicators of vascular-platelet and fibrinolytic links of the hemostasis system in viral hepatitis have a compensatory and adaptive orientation and contribute to maintaining homeostasis at different levels, but are closely related to the number and functional state of platelets.

Keywords: viral hepatitis. tooth extraction, vascular-platelet and fibrinolytic links of the hemostasis system.

One of the most frequent operations in surgical dentistry is the removal of teeth, which leads to the appearance of defects in the dentition, which require orthopedic treatment. It has been established that the main causes leading to complications and unsatisfactory quality of dental treatment after tooth extraction include: imperfection and insufficient information content of both clinical and instrumental laboratory methods of examination of patients, reduction in the perioperative period of complications caused by disorders of the hemostasis system. As is known, damage to the endothelium of a blood vessel during tooth extraction is an incentive to start the formation of a blood clot. The process of blood clot formation is closely related to liver function. Parenchymal liver cells produce most of the factors of the coagulation and fibrinolytic systems, as well as thrombopoietin, which is responsible for the production of platelets from megakaryocytes. In addition, the reticuloendothelial system of the liver provides clearance of activated forms of hemostatic factors. Changes in liver function in acute and chronic diseases initiate hemostatic abnormalities predisposing to the manifestation of bleeding or thrombosis.

Various aspects of hemostasis disorders associated with chronic liver diseases have been actively discussed in the scientific literature of the last decade. The reason for this is that the compensatory abilities of the blood clotting system are noticeably weakened in liver diseases. The opinion is expressed about the frequent predisposition of patients with liver pathology to hypercoagulation and thrombosis. At the same time, there are practically no works devoted to the study of the predictive role of hemostatic parameters in tooth extraction in patients with viral hepatitis. In this regard, the study of the clinical pathogenetic and prognostic significance of hemostatic homeostasis disorders during tooth extraction in chronic liver pathology is of undoubted theoretical and practical interest, since, on the one hand, it will clarify the features of hemostasis disorders and establish their relationship with the clinical manifestations of chronic liver diseases, and, on the other, enrich the arsenal of dentists with new criteria, which can be used to improve differential diagnostic and treatment programs and to form risk groups for the unfavorable course of liver pathology in surgical patients.

The purpose of this study was to assess the state of hemostatic homeostasis in the postoperative period after tooth extraction in patients with viral hepatitis.

Material and methods of research 58 patients with chronic viral hepatitis were examined. The studies were conducted in strict accordance with the requirements of biomedical ethics in accordance with the Geneva Convention on Human Rights (1997) and the Helsinki Declaration of the World Medical Association (2000) on the basis of the permission of the local ethics committee. In the group with chronic hepatitis, patients were distributed by gender as follows: men — 58%, women - 42%, the average age of patients was 35.6 ± 10.7 years. All patients received written voluntary informed consent to participate in the study. Inclusion criteria: verified diagnosis of

chronic viral hepatitis B and C detected by polymerase chain reaction (PCR) using a test system, patients who did not receive antiviral therapy. Exclusion criteria: patients under 18 years of age with concomitant viral hepatitis D or other diseases that cause liver damage, HIV infection, a history of pulmonary tuberculosis, autoimmune, oncological diseases, as well as pregnant women. In order to determine the control values of the studied parameters of the hemostasis system, 16 practically healthy individuals aged 25 to 45 years who gave informed consent to the examination, who did not differ from patients by gender and age, who did not have a history, the results of biochemical and serological studies of viral hepatitis, as well as other liver diseases, were examined. The work uses: instrumental studies: ultrasound examination of abdominal organs, clinical and laboratory methods. HCV-PHK indication, virus genotype determination, viral load level by polymerase chain reaction (PCR). A complete clinical and special examination of patients with HCV was carried out on an outpatient basis before surgery.

The examination included an analysis of complaints, anamnesis, objective research data; standard laboratory and instrumental studies were conducted. The number of platelets in the hematological analyzer was calculated in all examined patients, the adhesive and aggregation properties of platelets using an ADP inductor were determined visually using a phase contrast microscope according to Shitikova T.A. (1997). Determination of activated recalcification time (AVR) in plasma by the Clauss method was carried out according to a unified technique on the DiaMed CD 4 apparatus (Switzerland). Antithrombin-Sh (AT-Sh) was studied on an automatic digital photometer at a wavelength of 405 nm. [Barkagan Z.S. 2001]. Coagulometric method was used to determine the duration of prothrombin time, APTT using reagents of NPO RENAM (Russia). The platelet content was determined on an automatic analyzer "HT-2000i fSusmeh" (Japan).

Statistical processing of the obtained results was carried out using the applied analysis package of the Microsoft Excel 2002 tabular editor. The sample mean and the mean error ($M \pm m$) were calculated. The reliability of the differences for dependent and independent samples between the two averages was assessed by the Student's *t*-criterion. Differences in the compared indicators were taken as reliable results at $p < 0.05$

Research results and their discussion

After tooth extraction in patients with viral hepatitis, a hemostatic sponge and polycapran were used to stop bleeding. At the same time, it was found that after tooth extraction in the I-group of patients in 18 (45%) cases, bleeding from the hole of the removed tooth stopped within the next 10 minutes, and in the II-group of patients in 22 (55%) cases, bleeding occurred, which lasted for the first hour after tooth extraction. At the same time, thrombocytopenia (less than $100 \times 10^9/l$) was noted in group II patients, as well as an elongation of the onset of VSC to 5 minutes despite the use of a hemostatic sponge as a local hemostatic agent. In these cases, we replaced the hemostatic sponge with a polycapran, after which the bleeding from the hole of the removed tooth stopped within the next 10 minutes. Consequently, the use of a hemostatic sponge proved effective only when the level of platelets in peripheral blood was above $180 \times 10^9/l$, whereas with thrombocytopenia (less than $100 \times 10^9/l$), the hemostatic sponge was replaced by polycapran.

As is known, viral liver damage leads to complex disorders in the hemostasis system, but at the same time a balance is maintained between the coagulation and anticoagulation systems with a reduced reserve, and this balance is easily disturbed in one direction or the other, therefore, patients with chronic liver disease of viral etiology may develop not only bleeding, but also thrombosis. Therefore, we decided to assess the state of the vascular-platelet, plasma and fibrinolytic links of the system in the examined patients against the background of the use of a hemostatic sponge and polycapran, which will allow us to introduce in outpatient settings as prognostic tests to assess hemostatic homeostasis in the postoperative period during tooth extraction in patients with viral hepatitis.

I Evaluation of the vascular-platelet link of the hemostasis system after tooth extraction in two groups of patients with viral hepatitis

Considering that many of the studied factors of the coagulation system are synthesized in the endothelium and liver, we decided to study the effect of endothelial damage during tooth extraction on the parameters of the vascular-platelet link of the hemostasis system in patients with viral hepatitis

To do this, we studied the nature of changes in blood platelet content and activity, the level of activated recalcification time (AVR), a hemolysataggregational test evaluating the functional activity of platelets relative to the ADP inducer, as well as the activity of Willebrand factor and the content of antithrombin III in patients with viral hepatitis after tooth extraction.

As is known, about one third of patients with chronic liver diseases have thrombocytopenia (less than $100 \cdot 10^9/l$). They often have a reduced platelet aggregation capacity, which is due to a violation of the signal transduction mechanisms. As can be seen from the results of the study (table), the concentration of antithrombin III (AT III) synthesized by the liver and endothelium in the examined patients of group 2 after the manipulation decreases due to a decrease in synthesis and/ or an increase in consumption with hyperfibrinolysis, which is more pronounced in patients of group 2. At the same time, increased adsorption of platelets to the site deprived of endothelial lining, during tooth extraction in patients with viral hepatitis is accompanied by an increase in active forms of blood plates. The observed dynamics of the sum of active forms of platelets in patients with chronic viral hepatitis combined with thrombocytopenia tended to increase by an average of 1.9 times relative to the indicators of healthy individuals with intact periodontal disease. A significant number of active platelets are located not only in the lumen of the vessels of the oral mucosa, but also in the gum mucosa itself. This is one of the reasons for the activation of the atherogenic process at the site of destruction of the endothelium after tooth extraction in patients with viral hepatitis. After appropriate use in patients of group 2 of polycapran, it was possible to reduce the level of active forms of platelets.

Table 1

Indicators of the vascular-platelet link of the hemostasis system in patients with viral hepatitis before and after therapy

Indicators	Healthy n=16	Patients with viral hepatitis I-group n=18		Patients with viral hepatitis II-group n=22	
		before	after	before	after
The sum of active forms of platelets (%)	12,42±0,79	18,13±1,74*	16,57±1,13	20,13±1,34*	13,11±1,24
Platelet aggregation to ADP inducer Tma%	34,18±2,47	42,31±3,48*	39,14±3,03	47,69±3,53*	36,12±2,78
Activated recalcification time (sec)	57,81± 5,21	64,76±5,15	62,74± 5,43	72,07±6,13*	64,76±7,15
Antithrombin-III (%)	88,35±6,12	80,14±5,71	81,79±6,68	74,23±5,66	79,67±5,71

The Willebrand Factor (%)	81,37±4,56	88,59±7,13	85,73±7,04	92,89±7,84*	83,02±7,15
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Note: *-the reliability of differences P 0.05 relative to healthy individuals

At the site of surgery, there is also an effusion of red blood cells and its destruction, which leads to the release of platelet ADP-inducer from the erythrocyte, which enhances platelet aggregation. In patients with viral hepatitis, an increase in platelet aggregation activity on the effect of the ADP inducer (Tma) was noted by 1.5 times. Also, the therapy performed using polycapran contributed to a decrease in the aggregation properties of platelets to the ADP inducer. The observed prolongation of the activated recalcification time (AVR) by 1.4 times in patients with group 2 viral hepatitis indicates a deficiency of plasma factors (XII,XI,XIII) of the blood coagulation system and the process of hypocoaguration. Against this background, fibrinogen consumption coagulopathy is observed. After appropriate therapy, taking into account the platelet level, led to a reduction in the time of the activated recalcification time.

As is known, antithrombin-III is a specific protein of the blood coagulation system, which is synthesized in the vascular endothelium and in the liver. Its main function is to inactivate several major coagulation factors, including thrombin, and prevent the increased formation of blood clots-blood clots. In patients with viral hepatitis, especially in the second group, as shown in Table 1, there is a statistically significant decrease in the activity of antithrombin III compared to the control group, which reflects a decrease in its release by endothelial cells, as well as the index of anticoagulant activity of the vascular endothelium. Usually, antithrombin III helps regulate this process by slowing down the action of several coagulation factors, including thrombin, as well as factors X, IX and XI, designed to prevent the formation of excess blood clots. At the same time, a decrease in the level of antithrombin III, as shown in our studies, indicates the consumption of this anticoagulant, due to the activation of the hemostasis system. The use of polycapran in group 2 patients contributed to an increase in the level of antithrombin-III in the blood plasma of the examined individuals after surgery. Thus, the obtained research results indicate that tooth extraction in the examined patients, especially with combined thrombocytopenia, requires the use of polycapran instead of a hemostatic sponge, and at the same time, the diagnostic marker is an assessment of not only the number of platelets, but also the functional property of the blood plate.

II Evaluation of the fibrinolytic link of the hemostasis system after tooth extraction in patients with viral hepatitis

All proteins involved in the process of fibrinolysis; protein C, alpha-2-macroglobulin, antithrombin-III and representatives of the kallikrein system are synthesized in the liver. At the same time, the kallikrein-kinin system (KCS) plays a central role in regulating the activity of cascade proteolytic systems – kininogenesis, blood clotting, fibrinolysis, complement, renin-angiotensive system – and providing the processes of adaptation and protection of the body. This system, together with the renin-angiotensin-aldosterone system, regulates local microcirculation. In blood plasma, the activity of kallikrein is controlled by a2-macroglobulin and antithrombin III. Activation of precallikrein occurs due to its cleavage by activated Hageman factor (XIIa) on the surface of the damaged endothelium. This system activates fibrinolysis by converting plasminogen into plasmin, and also increases the secretion of IL-1, TNFa, IL-8, prostaglandins and leukotrienes. In our study, which is presented in Table 2, reliable signs of activation of the kallikrein-kinin system were revealed. The high activity of kallikrein in combination with a significant decrease in the blood content of its precursor, precallikrein, testified to the activation of the kallikrein—kinin system of the blood in patients with chronic viral hepatitis, which is often accompanied by a significant increase in fibrinolytic activity in the blood. Thus, the activity of kallikrein was increased by 1.7 times and the level of precallikrein was reduced by 10%. The use of polycapran in patients with viral hepatitis b after the surgical period allowed to reduce the level of kallikrein and increase precallikrein.

Indicators of the fibrinolytic link of the hemostasis system in patients with viral hepatitis before and after tooth extraction

Indicators	Healthy n=16	Patients with viral hepatitis I-group n=18		Patients with viral hepatitis II-group n=22	
		before	after	before	after
Kallikrein nmol / min / ml	71,56 ± 5,68	123,1 ± 9,27	108,1 ± 8,75	126,18 ± 9,27*	83,15 ± 7,27
Precallikrein nmol/min / ml	358,2 ± 13,45	321,3 ± 11,49	334,2 ± 11,68	319,35 ± 12,37	351,12 ± 10,6
Alpha-2- macroglobulin (mg/dl)	147,83 ± 7,51	281,91 ± 9,39*	267,5 ± 8,11*	284,91 ± 9,15*	162,54 ± 8,23
Activated partial thromboplastin time (sec)	30,56 ± 2,78	28,32 ± 2,14	32,12 ± 2,19	35,78 ± 2,53	30,14 ± 2,05

Note: *-the reliability of differences P 0.05 relative to healthy individuals

We found a regular coordinated activation of proteinase systems and a decrease in the level of the main kallikrein inhibitor -alpha2-macroglobulin, the value of which was increased by 99% before surgery compared with the norm in most of the examined patients. It should be noted that the observed prolongation in time of the APTT index in blood plasma before surgery in patients of group 2 indicates a violation of the activity of plasma hemostasis, due to the activation of the plasmin system.

Thus, the indicators of the vascular-platelet and fibrinolytic links of the hemostasis system in viral hepatitis have a compensatory and adaptive orientation and contribute to maintaining homeostasis at different levels, but are closely related to the number and functional state of platelets. At the same time, it is possible that the main influence on changes in hepatic blood flow in patients with chronic viral hepatitis has an increased level of kallikrein. The latter is one of the causes of excessive expansion of the precapillary bed, which contributes to slowing down blood flow in tissues and organs and exacerbates the state of hypoxia and hypoxemia. These are the pathogenetic basis for the occurrence of liver dysfunction. Consequently, patients with chronic viral liver pathology have a variety of hemostatic defects that affect all parts of the hemostasis system. Such patients have a narrow band of maintaining hemostatic balance, and the existing balance can easily be transformed into hypo- or hypercoagulation. This group of patients with surgical placement in the dental system may be one of the causes of the disorder, which is accompanied by increased bleeding, but in some patients the development of intravascular coagulation syndrome can lead to thrombotic episodes. Only comprehensive studies prior to surgical placement in the dental system, including simultaneous diagnosis of the main components of fibrinolysis and thrombosis of the blood clotting system, are able to give a general picture of the state of hemostasis and carry out preventive measures to prevent complications in this contingent of patients. In this situation, coagulological support for tooth extraction in patients with viral hepatitis should be differentiated, taking into account not only the indicators of the hemostasis system, but also the study of the activity of blood plasma platelets. It should be noted that timely laboratory detection of existing defects of the hemostasis system helps to prevent both hemorrhagic and thrombotic complications, improve the quality of life of patients and the results of treatment of

pathology of the dental system. It must be remembered that infection can be a trigger factor in the development of bleeding in this contingent of patients after tooth extraction.

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