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Hemostatic and Histopathological Effects of Local Mineral Zeolite and Tranexamic Acid in Experimental Femoral Artery Bleeding Model

Müzeyyen Seda Altop[1], Özge Özdal Zincir[2], Meral Ünür[3], Necat Vakur Olgaç[4], Sevgi Özyeğin[5]

[1] Okmeydani Oral and Dental Health Center, Department of Maxillofacial Surgery, Istanbul, Turkey
[2] Department of Maxillofacial Surgery, Faculty of Dentistry, Istanbul Gelisim University, Istanbul, Turkey
[3] Department of Oral and Maxillofacial Surgery, Faculty of Dentistry, Istanbul University, Istanbul, Turkey
[4] Department of Clinical Oncology, Oncology Institute, Istanbul University, Istanbul, Turkey
[5] Private Practise, Istanbul, Turkey

SUMMARY

Background/Aim: *This study aimed to evaluate the effect of local zeolite and tranexamic acid application on hemostasis duration and histopathological changes in the experimental bleeding model, created by puncturing femoral arteries in rats.* ***Material and Methods:*** *A total of 36 Sprague Dawley female rats weighing an average of 240 ± 20 g were used in the study. The three main study groups were the zeolite, zeolite+tranexamic acid, and control groups. Each group was sacrificed on the seventh and fourteenth days of the study, using subgroups for histopathological findings. After piercing the femoral artery of each rat, one gram of the material assigned to the group was applied to the bleeding site after which a 100-gram scale weight was placed on the site for 30 sec intervals, during which temperature was measured. The same sequence of procedures was repeated for the control group, using only standard compression. Statistical analysis was performed using IBM Statistical Package for Social Sciences (SPSS) 15 statistical software. Significance was evaluated at the level of p< 0.05.* ***Results****: The bleeding stop time of the control group was significantly longer than the zeolite and zeolite+tranexamic groups (p< 0.05). There was no statistically significant difference between the zeolite and zeolite+tranexamic groups' bleeding stop times (p> 0.05) or between the mean wound temperatures of the control and zeolite+tranexamic acid groups when bleeding stopped (p> 0.05).* ***Conclusions****: The effectiveness of the zeolite group and zeolite+tranexamic acid mixture is more than the control group in ensuring bleeding control. Their efficacy has been clearly observed in providing hemostasis. In addition, it has been determined that zeolite tranexamic acid mixture causes less exothermic reaction than zeolite group. We believe that this new formula should be developed and used to guide new studies.*

Key words: Mineral Zeolite, Tranexamic Acid, Hemorrhage Control, Topical Hemostat, Femoral Arterial Injury

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Introduction

A hemorrhage occurs when the blood circulating in the blood vessels exits because of the disruption of tissue integrity. Severe hemorrhaging can cause hypoxia, hypothermia, multiple organ failure, shock, and death, and it accounts for 33 to 50% of all traumatic deaths[1,2].

Bleeding control occurs through the body's hemostasis mechanism, which involves a series of reactions developed by the organism to stop bleeding during or after trauma. Normally, hemostasis occurs in four stages: the vasoconstrictive, platelet, and coagulation phases, followed by clot retraction[3,4,5].

Hemorrhage control is difficult when a patient has a bleeding tendency, usually caused by anticoagulants.

Traditional management entails the interruption of anticoagulant therapy for dental surgery to prevent hemorrhage. However, this practice may increase the risk of a potentially life-threatening thromboembolism. For this reason, research about how to stop bleeding with local agents has intensified in recent years[4].

The ideal hemostatic agent is simple to apply, biocompatible, effective, safe, achievable, and inexpensive[6]. Chitosan, oxidized cellulose, gelatin sponge, bone wax, thromboplastic agents, fibrin, fibrin glue, monsel solution, microporerous polysaccharide hemosphere, cyanoacrylates, silver nitrate, adrenaline, antifibrinolytic drugs, and mineral zeolite are agents frequently used to achieve local hemostasis[5]. Our research focused on mineral zeolite and tranexamic acid to balance each other's disadvantages. The effectiveness of tranexamic acid in local application is unclear, but it is simple to apply. The use of zeolite mineral has been increasing in recent years and it is known to cause an exothermic reaction. In our study, we made the tablet of tranexamic acid into powder, simulating its physical forms and making it miscible with zeolite.

Tranexamic acid (TA) is a synthetic antifibrinolytic drug that prevents the binding of plasminogen with fibrin and fibrinolysis[7]. Intravenous administration of tranexamic acid reduces bleeding during surgery. A systematic review of 129 randomised controlled trials, including 10.488 surgical patients, showed that tranexamic acid reduced the probability of receiving a blood transfusion by about one third (risk ratio 0.62, 95% confidence interval 0.58 to 0.65; P< 0.001), an effect that remained large when the analysis was restricted to high-quality trials[8].

However, its effect on the risk of thromboembolic events is uncertain and an increased risk remains a theoretical concern. Because there is less systemic absorption following topical administration. The direct application of tranexamic acid to the bleeding surface has the potential to reduce bleeding with minimal systemic effects[9].

In our study we also wanted to see the local effect of TA. If topical administration of tranexamic acid was shown to be a safe and effective way to reduce acute haemorrhage this would be of importance to global health.

Mineral zeolite is commonly used around world for different purposes. It consists of 65 to 85% calcium sodium aluminosilicate, 25 to 35% magnesium aluminosilicate, and quartz below the measurable limit. The fact that zeolite with the same chemical structure has different physicochemical properties can be explained through subgroups. The most used types of zeolite are sabbazite, clinoptilolite, and mordenite. When zeolite contacts blood, it rapidly absorbs water from blood and holds water molecules in the pores by using hydrogen bonds. Despite the significant efficacy of zeolite in hemostasis, its heat generation cannot be ignored[10,11]. How to balance the advantages and disadvantages is a challenge. Studies in the literature mostly focus on comparing the effectiveness of zeolite with other agents by inducing uncontrolled bleeding in animal models. Also zeolite is used in fatal injuries on the battlefield, especially in bandage form.

Our study aimed to compare the effectiveness of zeolite, and its mixed formula with tranexamic acid, by conducting tests on rats with severe femoral artery bleeding.

Material and Methods

Animal preparation

For our study, experimental animals were produced in the Istanbul Laboratory of Experimental Medicine Research Institute and the Experimental Animal Biology Department, and surgical procedures and care were performed in the same unit. A total of 36 Sprague Dawley female rats weighing an average of 240±20 g were used in the study. Experimental femoral artery injury study in rat models is envisaged as a suitable model, especially for short-term studies using many animals.

Experimental animals were housed in an automated room at 22±1º temperature that provided 12h of light and 12h of darkness. Rats were fed with standard rat food and drinking water containing 21% protein.

For animal experiments within the scope of this project, approval was obtained from the Istanbul University Experimental Medicine and Research Institute Experimental Animals Ethics Committee, dated 27.09.2012 and numbered 2012/120.

Study groups

In our study, subjects were divided into three main groups. The three main study groups were the zeolite, zeolite+tranexamic acid, and control group with 9% sodium chloride impregnated buffer. In addition, all study groups were divided into two subgroups according to the time the animals were sacrificed: 7 days later and 14 days later. Experimental animals were sacrificed under high anesthesia by intravenous NaTiopental 100 mg/kg. The study was carried out with 36 rats in total with 12 rats in each group and 6 rats in each subgroup.

Surgical and experimental procedures

In our research, the clinoptilolite form of zeolite extracted from İzmir region was used. The raw material of tranexamic acid is produced by Actavis pharmaceutical company in powder form and without additives. While preparing the tranexamic acid + zeolite group, 0.5 g zeolite and 0.5 g TA were mixed. Measurements were made with precision scales. Sterilization of packaged items after measurement was made under 25 gray gamma

ray by Gamma-Pak Sterilizasyon San. Tic. A.S for us to use. All surgical procedures were performed under intramuscular 10% ketamine HCl (50 mg/kg) and xylazine HCl (2.5 mg/kg) anesthesia. The animals in the groups were determined with a table of random numbers. For the surgical procedure, the rats were fixed on their backs and legs in a supine position. The right inguinal region of the rat was shaved and disinfected with an iodine solution. The skin and subcutaneous tissue were dissected, and the layers were passed. The artery and vena femoralis sheath were made visible, following which the sheath was dissected, and the artery and vein were separated. A 24-gauge branula needle pierced and perforated the isolated femoral artery. In the perforation area, one gram of zeolite was applied in group one, one gram of zeolite+tranexamic acid was applied in group two, and a 9% sodium chloride impregnated buffer was applied in the control group. Standard pressure was achieved by putting a constant weight of 100 g on the region immediately afterwards (Figure 1). From this moment, a stopwatch was used to determine bleeding time. After 30 sec, the weight was lifted, and bleeding control was performed. If hemostasis was achieved, a "+" was marked in the prepared bleeding timetable. The temperature of the perforation zone was measured with a laser thermometer and it was noted on the prepared heat exchange table. The same procedure was repeated every 30 sec until bleeding stopped. Bleeding time and temperature change were measured. If bleeding did not stop at 120 sec, the application was deemed "unsuccessful." After the measurements were made, the flap was restored, and the incision was closed with 3.0 silk stitches. The right inguinal regions of the experimental animals sacrificed on the 7th and 14th days were dissected and the study areas were removed for examination.

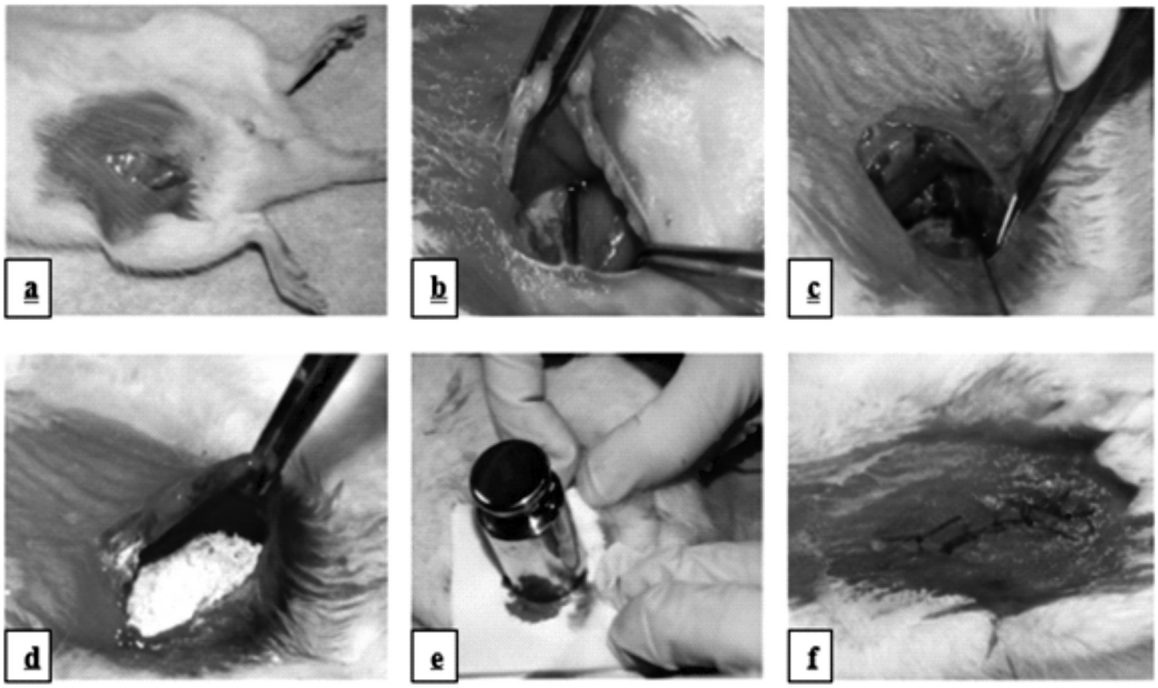

Figure 1. (a) Experimental study area (b) Femoral artery and vein view after dissection (c) Perforation with 24 gauge brancular needle (d) Local zeolite + tranexamic acid application (e) Standard pressure with 100 g weight (f) Suture of the defect region

Histopathological examination

The dissected tissues were fixed in a 10% formol solution for one week. After the material was routinely monitored, three-micron thick sections obtained from paraffin blocks were stained by a hematoxylin-eosin method and examined under a light microscope.

Sections were investigated to see whether there were thrombi in the femoral arteries and veins according to inflammation, necrosis, fibrosis, and foreign body reaction criteria.

Statistical analysis

While evaluating the findings obtained in the study, Statistical Package for Social Sciences (SPSS) for the Windows 15.0 program was used for statistical analysis. For quantitative data, the Oneway Anova test was used to compare the parameters that showed normal distribution, and the Tukey HDS test was used to determine groups that caused the differences. The Chi-Kare and Fisher's Exact Chi-Square tests were used to compare qualitative data. Significance was evaluated at the level of $p< 0.05$.

Results

Statistical evaluation of histopathological criteria

Inflammation

There was no animal loss during the experiment and follow-up. There was a statistically significant difference measured in the inflammatory levels of the seventh-day groups (p< 0.01). The inflammatory level of the control group on the seventh day was significantly lower than the zeolite (p: 0.002) and zeolite+tranexamic (p: 0.002) groups (p< 0.01). On the seventh day there was no statistically significant difference between the inflammation levels of the zeolite and zeolite+tranexamic acid groups (p: 0.121; p> 0.05). On the fourteenth day the inflammation level of the zeolite group was significantly higher than the zeolite+tranexamic acid (p: 0.002) and control groups (p: 0.002; p< 0.01). On the fourteenth day there was no statistically significant difference between inflammation levels in the zeolite+tranexamic acid and control groups (p: 1.000; p> 0.05). There was a statistically significant difference between the inflammation levels between the seventh and fourteenth days of the zeolite group (p< 0.01). On the seventh day in the zeolite group, the inflammation levels of all rats were above 60%, while on the fourteenth day the levels of inflammation decreased to between 30 and 60% in all rats (Table 1).

Table 1. Evaluation of inflammatory levels in the groups on the 7th and 14th days

	Inflammation	Zeolite	Zeolite + Tranexamic acid	Control	Total	
		n (%)	n (%)	n (%)	n (%)	
7th day	%5-30	0 (0)	0 (0)	6 (100)	6 (33.3)	
	%30-60	0 (0)	2 (33.3)	0 (0)	2 (11.1)	0.001**
	> %60	6 (100)	4 (66.7)	0 (0)	10 (55.6)	
14th day	%5-30	0 (0)	5 (83.3)	5 (83.3)	10 (55.6)	
	%30-60	6 (100)	0 (0)	0 (0)	6 (33.3)	0.001**
	> %60	0 (0)	1 (16.7)	1 (16.7)	2 (11.1)	

(p: pearson chi-square test ** p< 0.01)
(n: number of animals)

Necrosis

There was a statistically significant difference in the necrosis levels of seventh-day groups (p< 0.01). On the seventh day the necrosis level of the control group was significantly lower than the zeolite (p: 0.002) and zeolite+tranexamic acid (p: 0.002) groups (p< 0.01), but there was no statistically significant difference in the necrosis levels between the zeolite and zeolite+tranexamic groups (p: 1.000; p> 0.05).

On the seventh and fourteenth days there was a statistically significant difference in necrosis change levels between the zeolite and the zeolite+tranexamic groups (p< 0.01). While on the seventh day the necrosis levels of all rats were between 5 and 30%, on the fourteenth day the necrosis level decreased to between 0 and 5% in all rats (Table 2).

Table 2. Evaluation of necrosis levels in the groups on the 7th and 14th days

	Necrosis	Zeolite	Zeolite + Tranexamic acid	Control	Total	
		n (%)	n (%)	n (%)	n (%)	
7th day	%0-5	0 (0)	0 (0)	6 (100)	6 (33.3)	0.001**
	%5-30	6 (100)	6 (100)	0 (0)	12 (66.7)	
14th day	**%0-5**	6 (100)	6 (100)	6 (100)	18 (100)	1.000

(p: pearson chi-square test** p< 0.01)
(n: number of animals)

Table 3. Evaluation of fibrosis levels in the groups on the 7th and 14th days

	Fibrosis	Zeolite	Zeolite + Tranexamic acid	Control	Total	
		n (%)	n (%)	n (%)	n (%)	
7th day	%5-30	0 (0)	0 (0)	1 (16.7)	1 (5.6)	
	%30-60	5 (83.3)	4 (66.7)	5 (83.3)	14 (77.8)	0.387
	> %60	1 (16.7)	2 (33.3)	0 (0)	3 (16.7)	
14th day	**%30-60**	5 (83.3)	2 (33.3)	6 (100)	13 (72.2)	**0.027***
	> %60	1 (16.7)	4 (66.7)	0 (0)	5 (27.8)	

(p: pearson chi-square test * p< 0.05)
(n: number of animals)

Fibrosis

On the seventh day there was no statistically significant difference between any of the groups' fibrosis levels (p> 0.05). On the fourteenth day the fibrosis level of the zeolite+tranexamic group was found to be statistically significantly higher than the control group (p: 0.014; p< 0.05). There was no statistically significant difference between the seventh- and fourteenth-day fibrosis change levels in any of the three groups (p> 0.05; Table 3).

Foreign body reaction

On the seventh and fourteenth days there were statistically significant differences in rates of foreign body reaction between the groups (p< 0.01). In the zeolite and zeolite+tranexamic groups, foreign body reaction was observed in all samples. In contrast, no foreign body reaction was observed in the control group on the seventh and fourteenth days (Table 4).

Table 4. Evaluation of foreign body reaction incidence in the 7th and 14th days of the groups

	Foreign body reaction	Zeolite	Zeolite + Tranexamic acid	Control	Total	
	Reaction	n (%)	n (%)	n (%)	n (%)	
7th day	+	6 (100)	6 (100)	0 (0)	12 (66.7)	0.001**
	-	0 (0)	0 (0)	6 (100)	6 (33,3)	
14th day	+	6 (100)	6 (100)	0 (0)	12 (66.7)	0.001**
	-	0 (0)	0 (0)	6 (100)	6 (33.3)	

(p: pearson chi-square test ** p<0.01)
(n: number of animals)

Table 5. Evaluation of thrombus incidence in the 7th and 14th days of the groups

	Thrombus	Zeolite	Zeolite + Tranexamic acid	Control	Total	
		n (%)	n (%)	n (%)	n (%)	
7th day	+	0 (0)	2 (33.3)	0 (0)	2 (11.1)	0.105
	-	6 (100)	4 (66.7)	6 (100)	16 (88.9)	
14th day	+	0 (0)	0 (0)	0 (0)	0 (0)	-
	-	6 (100)	6 (100)	6 (100)	18 (100)	

(p: pearson chi-square test)
(n: number of animals)

Thrombus

On the seventh and fourteenth days there were no thrombi in the zeolite and control groups. On the seventh day in the zeolite+tranexamic acid group, the rate of thrombi was 33.3%, whereas on the fourteenth day no thrombi were seen (Table 5).

Statistical evaluation of bleeding stop time

There was a statistically significant difference between bleeding stop times among the groups (p< 0.01). The bleeding stop time of the control group was significantly longer than the zeolite (p: 0.001) and zeolite+tranexamic (p: 0.002) groups (p< 0.01). There was no statistically significant difference between the zeolite and zeolite+tranexamic groups bleeding stop times (p: 0.107; p> 0.05) (Table 6). However, when the experimental observations and scores were evaluated, the effectiveness of zeolite in providing hemostasis was found to be significantly higher than the modified formula.

Table 6. Evaluation of bleeding stop time

	Zeolite	**Zeolite+** TA	Control	Total	p
[1]**Bleeding stop Time (sec);** Ort±SS	42.50±23.79	67.50±31.66	112.50±31.66	74.17±40.87	**0.001****
[2]**30th sec stop;** n (%)	9 (75)	4 (33.3)	0 (0)	13 (36.1)	0.001**
[2]**60th sec stop;** n (%)	1 (33.3)	2 (25)	2 (16.7)	5 (21.7)	0.791
[2]**90th sec stop;** n (%)	2 (100)	5 (83.3)	2 (20)	9 (50)	0.016*
[3]**120th sec stop;** n (%)	-	1 (100)	5 (62.5)	6 (66.7)	1.000
150th sec stop; n (%)	-	-	3 (100)	3 (100)	-

[1]Oneway ANOVA test [2]Pearson Chi-Square test [3]Fisher's Exact test
**p< 0.01 *p< 0.05

There is a statistically significant difference between the groups with respect to the distribution of the animals whose bleeding stop time is 30 sec ($p< 0.01$). The rate of animals whose bleeding stopped at 30 sec was significantly higher in the zeolite group compared to the other groups. There is no statistically significant difference between the groups with respect to the distribution of the animals with the 60th second bleeding stopping time ($p> 0.05$). There is a statistically significant difference between the groups with respect to the distribution of the animals whose bleeding stop time is 90 sec ($p< 0.05$). The rate of animals whose bleeding stopped at 90 sec was significantly higher in the control group compared to the other groups. There is a statistically significant difference between the groups with respect to the distribution of the animals whose bleeding stop time is 90 sec ($p< 0.05$). The rate of animals whose bleeding stopped at 90 sec was significantly higher in the control group compared to the other groups. There is no statistically significant difference between the groups with respect to the distribution of the animals with the 120th second to stop bleeding ($p> 0.05$). Because all the animals with 150th second bleeding stopping time were in the control group, evaluation could not be made according to the groups.

Statistical evaluation of heat exchange occurring in wound

Table 7. Evaluation of temperature changes during the experiment

Temprature (ºC)	Zeolite avg	Zeolite+ TA	Control	p
[1]When bleeding stop	32.75±0.94	31.55±0.61	31.57±0.59	**0.001****
[1]30th sec	33.05±1.02	32.0±0.65	31.92±1.23	**0.014***
60th sec	˙32.17±0.25	31.91±0.61	32.10±1.16	
90th sec	˙32.25±0.78	31.52±0.69	31.79±0.55	
120th sec	-	¨30.90	31.87±0.57	
150th sec	-	-	˙32.37±0.46	

Oneway ANOVA test ˙n< 5 ¨n= 1
*p< 0.05 **p< 0.01

Discussion

Bleeding is one of the main problems that occurs during surgical procedures and may prolong both surgeries and postoperative complications. In recent years, studies reported a number of new powders capable of inducing hemostasis based on the molecular sieve mechanism. However, none of these products could meet the criteria for ideal hemostatic powders. Therefore, the search for a local hemostatic agent continues[12,13].

Costa *et al.*[14] performed a systematized literature review for local hemostasis in oral surgical procedures in patients using anticoagulants. In the study, 171 of 3861 patients using anticoagulants had bleeding complications after oral surgery. They emphasized that tranexamic acid was used most frequently to provide local hemostasis. Loomba *et al.*[15] carried out enucleation for three days after drug discontinuation in a 72-year-old patient who used long-term, low-dose aspirin with a dentigerous cyst. After the operation, a 10% tranexamic acid impregnated buffer was applied to the operation area for 30 min. There were no bleeding complications. In their study, Perdigao *et al.*[16] examined the effect of post-extraction bleeding control and tranexamic acid in patients scheduled for liver transplants. As a result of this study, the effectiveness of tranexamic acid in stopping postoperative bleeding, compared to the control group, was not significant. In our study, we found that the tranexamic acid group was effective in achieving hemostasis, compared to the control group.

In a study by Pederson *et al.*[17], 39 patients who received anticoagulant treatment did not make any changes in their medication doses before and after oral surgery. After operations, the affected area was irrigated with 10 ml of 4.8% tranexamic acid solution in 19 patients and placebo solution in 20 patients before suturing. During the seven days following operation, patients gargled with solutions four times a day for two minutes. Postoperative bleeding occurred in eight patients in the control group and one patient in the tranexamic acid group. As a result, in parallel with our findings, the effectiveness of local use of tranexamic acid in hemostasis was emphasized.

The hemostatic effectiveness of granular mineral zeolite has been recently demonstrated and approved by the FDA for use in 2002. It has reportedly been used after injuries in the Afghanistan and Iraq wars. It was released under the name QuikClot™ (QCG). It has been stated that it can cause tissue damage due to a high thermal effect in the application area. Ahuja *et al.*[18] have reported a new form of QuickClot™ Advances Clotting Sponge (ACS +) that balances clotting and heat. It is stated that the new formula, which is known to be effective in animal experiments, but which is impeded by heat production, reduces heat production, and does not cause histological damage. Arnaud *et al.*[19] examined the exothermic reaction development and the effectiveness of hemorrhagic agent QuickClot™ containing zeolite and its formula ACS + developed to prevent heat formation and bleeding. In a study of 15 pigs, vital signs and temperature change were measured with standard compression after bleeding in the femoral area. It was reported that the modified zeolite had fewer side effects and generated excessive heat. Similarly,

in our study, we found that the tranexamic acid formula of zeolite released lower levels of heat.

In the study of Johnson *et al.*[20], the bleeding efficacy of zeolite on 22 pigs was compared with a control group. Secondary bleeding and hemorrhage control were evaluated after injuring femoral arteries and veins in 11 pigs within each group. After one minute of free bleeding, following the incision, zeolite was applied to the wound area of subjects in the study group while no substance was applied in the control group. Standard pressure was applied to the study area after five minutes of direct pressure. Secondary bleeding was observed in the study area for five minutes, at the end of a 30 min period. As a result of the experiment, as in our study, zeolite was shown to be significantly effective in stopping bleeding, compared to the control group.

In a prospective experimental animal study conducted on 22 pigs, Gegel *et al.*[21] examined the effectiveness of hemostasis in motion by comparing QCG with a control group. Standardization was achieved between clotting time, weight, body temperature, arterial blood pressure, and total blood volume among the groups. As a result, it was emphasized that, like our study, QCG provided hemostasis on the move and inactive significantly compared to the control group and could be used effectively to treat war injuries.

In their study, Haasch *et al.*[22] histologically evaluated the effect of two hemostatic agents containing cellulose and collagen on bone in the tibia of 42 male rats. Although the inflammation cellulose-containing agent occurred more frequently during the seventh day of the study, there was no significant difference between the group receiving the collagen-based substance and the control group. On the fourteenth postoperative day, it was reported that most of the cellulose-based substance was in the cavity and that tissue healing was decreased. In our study, on the seventh day, the inflammatory level of the control group was significantly lower than in the zeolite and zeolite+tranexamic groups. On the fourteenth day, the inflammation level of the zeolite group was significantly higher than in the zeolite+tranexamic acid and control groups. Inflammation depends on the normal tissue reaction formed by the applied materials; however, the level of inflammation in the zeolite group was found to be significantly higher. We think that fibrosis formation, one of the other parameters we examined in our study, may be caused by chronic proliferative inflammation due to foreign body reaction in the tissue. However, in order to reach a clear view on this issue, the decrease in fibrosis level should be evaluated after long-term follow-up. Our other parameter, foreign body reaction, indicates that wound healing may be delayed. However, prevention of bleeding complications is vital compared to wound healing, especially in post-traumatic and emergency situations and in patients using anticoagulants.

Blood coagulation is a dynamic process involving fibrin formation and fibrin dissolution. Fibrin is easily dissolved by the fibrinolytic enzyme in the early stage of blood clotting. The available hemostatic materials focus primarily on accelerating the formation of blood clots, but they ignore the effect of the fibrinolytic system on coagulation. Inhibition of fibrinolysis is also critical for promoting coagulation, but hemostatic agents that combine rapid clot formation with effective inhibition of fibrinolysis have been reported rarely[23]. Tranexamic acid is a synthetic anti-fibrinolytic drug and similar to lysine in structure. TA can competitively inhibit the adsorption of plasminogen and lysine binding sites on fibrin, protecting fibrin from being degraded or dissolved by fibrinolytic enzymes[24,25]

The zeolite mineral we prefer in our study works like a molecular sieve and absorbs water. This exothermic reaction develops as a completely physiological reaction, not a chemical one. Blood is concentrated by plasma absorption. Platelets and coagulation factors are allowed to form clots much faster[10,11]. The introduction of TA had no influence on water absorption of zeolite.

Therefore, our study aimed to combine the rapid liquid absorption of zeolite with the fibrinolysis inhibition effect of TA to create an advantageous hemostatic agent prototype. The bleeding stop times in the zeolite and zeolite+tranexamic acid groups were statistically significantly shorter than in the control group. The fact that there is no statistically significant difference between the zeolite and zeolite+tranexamic groups bleeding stop times shows that the combination formula is preferable due to its advantage in heat production.

Conclusions

The benefits of using clinoptilolite as a hemostatic agent include easy sterilization and positive antibacterial properties. Nevertheless the formula we combined was more effective because it is less damaging to tissue, generates less heat, and provides hemostasis. Although our study is the first in which zeolite and tranexamic acid were used together, our data suggests that this combination can be investigated in many ways and that more successful results can be achieved. In addition, we believe that the number of experimental studies investigating the effects of materials on bone should increase in order to achieve local hemostasis in oral surgery.

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Correspondence:

Seda Altop
Department of Maxillofacial Surgery
Okmeydani Oral and Dental Health Center
Istanbul, Turkey
e-mail: sedaaltop@gmail.com