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Experimental testing of tannic acid target delivery system for correcting periodontal microcirculation

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Abstract:
Objective: to study the effect of the targeted delivery system of tannic acid (TA) in silver alginate microcapsules on the state of gum microvasculature in rats with intact periodontium vs. experimental periodontitis.
Materials and Methods. The study was conducted on 90 white rats, distributed among six groups: the control group, two groups with intact periodontium and single application of gel with microcapsules loaded/not loaded with TA, experimental periodontitis group, and two groups of animals with periodontitis and repeated application of gel with microcapsules loaded/not loaded with TA. We assessed gingival perfusion and blood flow modulation mechanisms in rats via laser Doppler flowmetry.
Results. Applying gel with silver microcapsules to an intact gum in rats caused 7.5% transient increase in perfusion and activation of microcirculation modulation. Loading microcapsules with TA reduced the severity of transient microcirculatory changes. Using gel with TA-loaded capsules in rats with periodontitis allowed achieving a more pronounced normalization of perfusion and mechanisms of microcirculation modulation vs. using gel containing microcapsules without active components.
Conclusion. Loading alginate microcapsules with silver ions and TA yielded reduction of the irritating effect on gingival mucosa accompanied by an increase in the effectiveness of correcting microcirculatory disorders in periodontitis.

Keywords: periodontitis, microcirculation, tannic acid.

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Introduction

The Centers for Disease Control and Prevention consistently report a high prevalence of various forms of periodontitis among 47% of people aged 30 and over. Periodontal disease is accompanied by systemic inflammation associated with many chronic diseases [1]. Recent advances in nanotechnology allowed developing new therapeutic materials for treating periodontitis [2, 3]. Extensive studies revealed high antibacterial activity of silver nanoparticles (AgNP) against a wide range of pathogenic microorganisms, including those causing periodontal disease. AgNP nanoparticles are successfully used in other areas of dentistry to prevent the formation of biofilms on the surface of dental biomaterials [4]. A variety of approaches to the synthesis of polymer/AgNPs complexes has improved the therapeutic function of nanoparticles and their application in clinical practice [5]. Many studies have demonstrated a high efficacy of AgNPs in the treatment of microbial infections [6, 7], which determines the prospects for their use in treating chronic generalized periodontitis, the main etiological factor of which is periodontopathogenic bacteria.

Currently, the correction of microcirculation in the gums as the basis of pathogenetic therapy remains a difficult task, in which preparations with antioxidant properties demonstrate some effectiveness [8]. Tannic acid (TA) is among the most widespread polyphenols combining anti-inflammatory and antioxidant properties. TA was employed to improve wound healing, inhibit pathogen adhesion, and provide antibacterial effect [9, 10]. Therefore, TA in the composition of therapeutic agents could help suppressing microbial pathogens of the periodontal pocket and prevent the destruction of periodontal tissues, which is of particular interest for using these preparations in dental practice. Progress in periodontitis treatment could be achieved with a single therapeutic agent that combines the properties of plant-derived polyphenols and AgNPs.

The development of various targeted drug delivery systems has become especially important in solving a number of problems [11, 12]. Multicomponent and multifunctional structures, such as microcapsules, could provide necessary optimization of medicine release kinetics, including prolongation of its therapeutic action. The use of such delivery systems, based on microcapsules, in anti-inflammatory therapy could improve both the effectiveness of medicines and the treatment of periodontitis in general [13].

The objective of our study was to evaluate the effect of a targeted delivery system of TA preparations in the composition of silver alginate microcapsules on the state of

gum microvasculature in white rats with intact periodontium vs. experimental periodontitis.

Materials and Methods

The research was performed on 90 white male rats weighing 200–250 g. Animals were kept under standard vivarium conditions with natural light and free access to water and food. Our study complied with the provisions of the European Convention for the Protection of Vertebrate Animals and the requirements of the national guidelines for maintenance and care of laboratory animals. Ten minutes prior to manipulation, animals were anesthetized by intramuscular administration of Telazol® (Zoetis Inc., Spain) at a rate of 0.1 mL/kg and Xylanit® (LLC Nita-Pharm, Russia) at a dose of 1 mg/kg of animal weight.

Modeling of periodontitis in rats was performed by the ligature method [14]. We used a modification of the method by A. Ionel et al. [14], which allowed simulating periodontitis in the area of lower incisors, easily accessible for gel applications and microvasculature condition monitoring. Under anesthesia, a polyfilament non-absorbable suture was stitched into the gum in the region of mandibular incisors. On day 14 after suturing, the ligature was removed.

Study animals were distributed among six groups of 15 animals each. Group 1 was represented by control animals with intact periodontium. Group 2 included rats subjected to a single application of 10 μL of a gel containing microcapsules of silver alginate without TA onto an intact gum; monitoring of microcirculation parameters was carried out one hour and 24 hours after gel application. Group 3 comprised rats with intact periodontium, which were subjected to a single 10 μL application of a gel containing microcapsules of silver alginate filled with TA; monitoring of microcirculation parameters was carried out one hour and 24 hours after gel application. Group 4 could be defined as comparative: it consisted of animals with experimental periodontitis, which were subjected to repeated application of 10 μL of saline onto an inflamed gum surface on days 14, 16 and 18 of the experiment after the ligature removal. Group 5 that could be defined as experimental group No. 1, encompassed rats with a modeled periodontitis: after ligation, they were subjected to repeated application of 10 μL of a gel containing microcapsules of silver alginate without TA. Group 6, also known as experimental group No. 2, included rats with experimental periodontitis, in which a gel containing microcapsules loaded with TA was applied to the inflamed mucosa on days 14, 16, and 18 after ligation.

Animals with intact periodontium and experimental periodontitis underwent applications of alginate silver microcapsules with or without TA loading on the gums in the region of lower central incisors. In rats with experimental periodontitis, the gel was applied three times: on days 14, 16, and 18 of the experiment. Microcapsules were prepared according to the protocol published earlier [15].

Monitoring of gingival perfusion parameters in rats was performed via laser Doppler flowmetry on a LAKK-OP analyzer (Lazma Scientific Production Enterprise, Russia). For laser Doppler flowmetry measurements, the LAKK transducer was placed in the gingiva at a point located between both anterior incisors of the lower jaw from the vestibular side. Gingival perfusion was registered for 8 minutes. In the course of our research, perfusion index was evaluated, reflecting the change in blood perfusion of the microvasculature of the study area. Normalized amplitudes of perfusion oscillations in the main regulatory frequency ranges included endothelial, characterizing the state of the vascular endothelium; neurogenic, reflecting peripheral resistance of arterioles; myogenic, responsible for assessing the state of the muscle tone of precapillaries; respiratory, reflecting the outflow of blood; and cardiac, describing the inflow of arterial blood into the microvascular bed. Calculation of the amplitudes of perfusion oscillations in indicated ranges was carried out via wavelet analysis; the normalized values were determined as ratios of absolute values of the oscillation amplitudes to threefold standard deviation of perfusion.

The obtained experimental data were processed using the Statistica 10 software (StatSoft, USA). The normality of data distributions was tested using the Shapiro-Wilk criterion W. Most of our data did not comply with the normal distribution law. Consequently, the comparison of experimental values was carried out via Mann-Whitney U test. This model was also used to calculate Z criterion and p-values: the latter below 0.05 were considered statistically significant. Our data are presented in tables as a median and interquartile range: Me (Q25; Q75).

Results

An hour later after applying a gel containing alginate microcapsules with silver nanoparticles to intact gums, we observed a statistically significant increase in perfusion by 7.5%, compared with the control group. An increase in perfusion was accompanied by a change in the active mechanisms of microcirculation modulation, mainly due to an increase in the amplitude of neurogenic and myogenic oscillations. The change in these parameters indicated a decline in neuro- and myogenic tones, as well as peripheral resistance in the precapillary link of the microvasculature. There were no statistically significant changes in the amplitude of endothelial oscillations in blood flow.

Changes in the parameters of passive mechanisms of blood flow modulation were manifested by an increase in the normalized amplitudes of cardiac and respiratory oscillations, reflecting an increase in arterial blood inflow and a deterioration in blood outflow in the microvasculature, which indicated the development of mixed gingival hyperemia.

After 24 hours, perfusion returned to the normal level; however, an increase in normalized amplitudes of myogenic, respiratory and cardiac oscillations vs. the intact control animas remained. Besides, 24 hours after applying gel containing alginate microcapsules with silver nanoparticles onto intact mucosa, the animals exhibited a statistically significant increase in the normalized amplitudes of endothelial oscillations, compared with the control group, which implied a reduction in the endothelium-dependent component of arteriole tone.

Hence, applying gel, containing alginate microcapsules with silver nanoparticles, resulted in a weak irritating effect on intact gingiva in rats. The latter was manifested by a short-term intensification of perfusion and was associated with more persistent changes in blood flow modulation, characterized by an increase in neurogenic and myogenic tone of the vessels in precapillary microcirculation (*Table 1*).

No significant changes in the perfusion index were noted after applying the gel containing alginate capsules with silver nanoparticles loaded with TA. An hour after exposure, the amplitudes of neurogenic, myogenic, respiratory, and cardiac

oscillations were increasing. However, these changes in the microcirculation modulation were transient and completely leveled off 24 hours after the application of capsules with TA, with the exception of the normalized amplitudes of cardiac oscillations, the increased value of which reflected the preservation of an increased inflow of arterial blood into the microvasculature (*Table 1*).

When comparing the irritating effects of the developed gel compositions, we discovered that one hour after the application of capsules containing TA, the perfusion parameters were lower than in the group of rats treated with the gel containing capsules without TA. There were no significant differences in the parameters of active and passive blood flow modulations. Twenty-four hours after application of the gel with alginate capsules loaded with TA, the perfusion of the gingival microvasculature was statistically significantly higher than in rats that received the application of the gel without TA. However, the amplitudes of myogenic oscillations, were significantly lower in the group of animals, in which the gel with capsules containing TA was applied onto the gums.

Table 1. Changes in gingival microcirculation parameters in white rats with intact periodontium after applying gel containing alginate microcapsules with silver nanoparticles loaded/not loaded with tannic acid, Me (Q25; Q75)

Parameters	Control (n=15)	Microcapsules with silver nanoparticles			
		Loaded with tannic acid		Not loaded with tannic acid	
		one hour after exposure (n=15)	24 hours after exposure (n=15)	one hour after exposure (n=15)	24 hours after exposure (n=15)
Perfusion index, perfusion units	20.1 (19.1; 21.0)	21.6 (21.1; 22.4) p_1<0.001	19.7 (19.5; 20.2) p_1=0.860	20.3 (19.9; 20.7) p_1=0.434 p_2<0.001	20.4 (20.3; 20.7) p_1=0.347 p_2=0.032
Oscillation amplitude, conventional units: endothelial	9.4 (7.8; 13.3)	11.1 (8.8; 12.3) p_1=0.234	11.6 (10.6; 15.4) p_1=0.037	9.3 (8.5; 11.0) p_1=0.563 p_2=0.407	9.4 (8.1; 12.7) p_1=0.882 p_2=0.097
neurogenic	10.7 (8.5; 12.3)	12.2 (11.1; 13.7) p_1=0.015	12.0 (10.4; 12.5) p_1=0.061	12.1 (11.2; 12.9) p_1=0.028 p_2=0.747	11.2 (9.7; 12.6) p_1=0.448 p_2=0.289
myogenic	10.4 (8.1; 11.9)	13.8 (10.4; 14.9) p_1=0.002	12.9 (12.3; 13.9) p_1<0.001	13.3 (12.4; 14.6) p_1<0.001 p_2=0.963	11.3 (9.9; 13.4) p_1=0.150 p_2=0.030
respiratory	8.1 (5.9; 9.1)	10.5 (8.8; 11.7) p_1<0.001	9.8 (9.2; 11.8) p_1<0.001	10.6 (9.6; 11.7) p_1<0.001 p_2=0.782	8.6 (8.1; 10.6) p_1=0.064 p_2=0.181
cardiac	5.3 (3.6; 6.3)	7.2 (6.0; 7.5) p_1<0.001	6.8 (5.9; 7.1) p_1=0.002	6.7 (5.9; 7.4) p_1<0.001 p_2=0.853	6.1 (5.1; 7.0) p_1=0.042 p_2=0.381

p_1 – vs. the control, p_2 – vs. the capsules not loaded with tannic acid.

Hence, changes in the microcirculation of the gums, whenever the gel containing capsules loaded with TA was applied, were not pronounced. Therefore, loading TA into the alginate capsules with silver nanoparticles allowed reducing the irritating effect on the gums (*Table 1*).

When modeling periodontitis in rats on the second week after ligation, there was a statistically significant increase in the perfusion index by 1.2 times. At the same time, changes in the active modulation of microcirculation were revealed, manifested by a statistically significant increase in the amplitudes of myogenic oscillations, which indicated a decline in the tone of precapillary sphincters and an upsurge in the intensity of nutritional blood flow. In addition, we detected an increase in the amplitudes of passive oscillations in blood flow, both respiratory and cardiac, which, combined with an increase in the perfusion index, reflected the development of mixed gingival hyperemia (*Table 2*).

On the third week of the experiment, when modeling periodontitis in rats, there was a further increase in the perfusion index. The value of gum perfusion in rats of the comparison group was 37.3% higher than the average value of the intact control animals. At the same time, perfusion significantly exceeded the values recorded in rats on the second week of the experiment. Disorders of microcirculation modulation on the third week were more pronounced vs. the second week, and were manifested by a statistically significant increase of amplitudes in all regulatory ranges. Also, a statistically significant increase in the amplitudes of endothelial and neurogenic oscillations was noted, compared with the second week of the experiment (*Table 2*).

Table 2. Dynamics of changes in gingival microcirculation parameters in rats with experimental periodontitis, Me (Q25; Q75)

Parameters	Control (n=15)	Periodontitis	
		2 weeks (n=15)	3 weeks (n=15)
Perfusion index, perfusion units	20.1 (19.1; 21.0)	24.8 (23.9; 25.7) p_1<0.001	27.6 (24.0; 28.2) p_1<0.001 p_2=0.016
Oscillation amplitude, conventional units: endothelial	9.4 (7.8; 13.3)	10.6 (9.5; 11.8) p_1=0.306	12.3 (10.2; 15.2) p_1=0.012 p_2=0.011
neurogenic	10.7 (8.5; 12.3)	11.0 (9.0; 13.2) p_1=0.414	12.8 (12.1; 14.3) p_1<0.001 p_2=0.019
myogenic	10.4 (8.1; 11.9)	14.0 (11.3; 15.4) p_1<0.001	12.9 (12.4; 14.3) p_1<0.001 p_2=0.633
respiratory	8.1 (5.9; 9.1)	9.5 (7.9; 11.1) p_1=0.002	10.1 (9.4; 10.8) p_1<0.001 p_2=0.678
cardiac	5.3 (3.6; 6.3)	6.5 (5.5; 7.4) p_1=0.002	6.4 (5.9; 7.0) p_1<0.001 p_2=0.966

p_1 – vs. the control, p_2 – vs. periodontitis (2 weeks), p_3 – vs. periodontitis (3 weeks).

Thus, in ligated rats of the comparison group, the inflammatory changes in the blood flow of the gums developed during the second week of the experiment and intensified by the third week, which implied the chronic nature of the alteration in the periodontal microcirculation.

In rats with periodontitis, after a course of gel applications with alginate capsules containing silver nanoparticles without TA, the perfusion index significantly declined relative to animals of the comparison group that did not undergo correction of microcirculatory disorders but remained above the level of intact control. At the same time, there were changes in the active modulation of blood flow, manifested by a reduction in the amplitude of endothelial oscillations relative to the comparison group, reflecting an increase in the endothelium-dependent component of arteriole tone. It should be noted that the amplitudes of myogenic and respiratory oscillations during the application of capsules without TA significantly exceeded the values in intact control animals and did not differ from those in animals of the comparison group, which implied that the decrease in the myogenic tone of precapillary sphincters and presence of venous hyperemia in the microcirculatory bed persisted (*Table 3*).

Table 3. Effect of tannic acid on changes in gingival microcirculation parameters in rats with experimental periodontitis, Me (Q25; Q75)

Parameters	Control (n=15)	Periodontitis (n=15)	Periodontitis + gel with capsules (n=15)	Periodontitis + gel with TA-loaded capsules (n=15)
Perfusion index, perfusion units	20.1 (19.1; 21.0)	27.6 (24.0; 28.2) p_1<0.001	24.6 (22.7; 27.0) p_1<0.001 p_2=0.016	23.6 (23.3; 24.0) p_1<0.001 p_2<0.001 p_3=0.383
Oscillation amplitude, conventional units: endothelial	9.4 (7.8; 13.3)	12.3 (10.2; 15.2) p_1=0.012	10.3 (9.1; 12.1) p_1=0.390 p_2=0.031	10.0 (5.9; 12.9) p_1=0.942 p_2=0.056 p_3=0.678
neurogenic	10.7 (8.5; 12.3)	12.8 (12.1; 14.3) p_1<0.001	12.3 (10.0; 13.7) p_1=0.053 p_2=0.262	8.4 (7.3; 12.4) p_1=0.488 p_2=0.004 p_3=0.027
myogenic	10.4 (8.1; 11.9)	12.9 (12.4; 14.3) p_1<0.001	12.7 (10.6; 14.8) p_1=0.005 p_2=0.319	8.4 (6.6; 12.9) p_1=0.528 p_2=0.002 p_3=0.014
respiratory	8.1 (5.9; 9.1)	10.1 (9.4; 10.8) p_1<0.001	9.9 (7.2; 10.9) p_1=0.015 p_2=0.455	7.5 (4.3; 9.7) p_1=0.702 p_2=0.003 p_3=0.027
cardiac	5.3 (3.6; 6.3)	6.4 (5.9; 7.0) p_1<0.001	6.1 (5.1; 7.4) p_1=0.055 p_2=0.229	4.2 (3.5; 6.9) p_1=0.991 p_2=0.046 p_3=0.105

TA – tannic acid, p_1 – vs. the control, p_2 – vs. periodontitis (3 weeks), p_3 – vs. capsules without TA (3 weeks).

Under the impact of the course of gel applications with alginate capsules containing silver nanoparticles loaded with TA, a more pronounced decrease in the perfusion index was observed in animals with periodontitis vs. using the gel without TA. Wavelet analysis of the variable component of perfusion in experimental group animals revealed a reduction in the normalized amplitudes of neuro- and myogenic oscillations relative to those in the rats of the comparison group, which reflected the effective correction of neuro- and myogenic tones of the vessels in the precapillary link of the microvasculature, characteristic of experimental periodontitis. Simultaneously, the experimental group animals demonstrated a decrease in the amplitudes of respiratory and cardiac oscillations, characterizing the outflow and inflow of blood into the vessels of the microcirculation. No significant changes in the parameters of active and passive mechanisms of microcirculation regulation were detected in the experimental group rats vs. the intact control, which indicated a complete restoration of adequate microcirculation modulation. When comparing the effect of the studied gels, we established that using capsules containing TA allows achieving a more pronounced normalization in the amplitudes of myogenic, neurogenic, and respiratory oscillations in animals with experimental periodontitis (*Table 3*).

Hence, loading TA into alginate capsules with silver nanoparticles yielded an increase in the effectiveness of correcting gingival perfusion, neurogenic tone of arterioles, myogenic tone of precapillary sphincters, and parameters of blood outflow from the microcirculation system in animals with experimental periodontitis.

Discussion

The state of the vascular bed is one of the defining aspects of pathological processes in the periodontium. Microcirculation plays a key role in the trophic supply of tissues and compensatory processes in the development of both inflammatory and ischemic lesions of periodontal tissues. Successful correction of chronic microvascular disorders requires extended release of vasoactive substances, which could be achieved by using a drug delivery system based on silver alginate microcapsules with a high ability to load a number of biologically active substances, including an anti-inflammatory agent, TA.

Among the most important parts of experimental testing of the developed microcapsule-based drug delivery system was the detection of potential side effects caused by the components of the system, including irritant effects. Experimental data indicated that the use of TA-free microcapsules had a weak irritant effect on intact gums in albino rats. Irritation manifested itself in a short-term increase of the perfusion index and was associated with more persistent changes in blood flow modulation caused by the reduction in the endothelium-dependent neuro- and myogenic components in the vascular tone of the precapillary microcirculation. The irritant effect was probably caused by silver nanoparticles, which was previously specified in some published sources [16, 17].

There were no changes in gingival perfusion after the use of microcapsules loaded with TA. In addition, the inclusion of TA in the composition of capsules reduced the severity of changes in the amplitudes of endothelial and myogenic oscillations after applying the gel. An increase of these amplitudes was among the characteristic signs of hyperemia

during inflammation. Therefore, a decline in the irritating effect on the gums may be due to the presence of anti-inflammatory properties in TA, described earlier in the literature [18, 19].

In the comparison group, inflammatory changes in the gingival blood flow occurred after ligation, which was recorded on day 14 of the experiment. These data correspond to the results published earlier by A. Ionel et al. [14], who demonstrated the presence of inflammation, as well as bone resorption on the 14th day after applying ligatures in the lower frontal group of teeth. Besides, it was established that microvascular disorders in the gums of rats progressed after ligature removal and exhibited an increased intensity on the 21st day, compared with the day 14, which was indicative of the persistent nature of microcirculatory disorder.

The use of microcapsules without TA on an experimental model of periodontitis in animals of Group 5 yielded a decline in the perfusion index, compared with animals of Group 4. This finding implied a positive effect of microcapsules on microvascular disorders. Previously, it was shown that silver nanoparticles in complex with polymers had pronounced antibacterial properties [20]. Considering the role of the microbial factor in the pathogenesis of microcirculatory disorders in periodontitis, partial normalization of perfusion under the impact of the developed gel may be associated with antibacterial effects of silver nanoparticles in microcapsules. However, when using the control suspension of microcapsules, the amplitudes of myogenic and respiratory oscillations significantly exceeded the values of the intact control and did not differ from those in the comparison group. This finding confirmed a persistent decrease in the myogenic tone of precapillary sphincters and hyperemia of microvessels, which could be associated with low anti-inflammatory activity and irritant effects found in intact rats after the use of TA-free microcapsules.

Comparison of the studied microcapsules with and without TA demonstrated that microcapsules loaded with TA could achieve higher efficacy in normalizing the amplitudes of myogenic, neurogenic, and respiratory oscillations in an experimental model of periodontitis. The presence of TA immobilized in microcapsules of silver alginate improved the effectiveness of gingival perfusion correction, neurogenic tone of arterioles, myogenic tone of precapillary sphincters, and parameters of blood outflow from the microcirculation system in experimental periodontitis. The positive effect of TA in the composition of the developed gels can be explained by the antibacterial and anti-inflammatory effects of polyphenols. For instance, it was established that polyphenols had a selective effect on periodontopathogenic microorganisms, especially Porphyromonas gingivalis, causing a reduction in the level of circulating IL-1β, TNF-α and IL-17 inflammatory cytokines. These cytokines are recognized triggers of inflammation and disease progression in periodontitis. Polyphenols could also reduce the extent of immune cell infiltration caused by bacteria, which may help mitigate further inflammatory damage. These bioactive compounds modulate the expression of genes associated with osteoclasts, which contributes to a decrease in the activity of the latter and reduce bone loss in rats with experimental periodontitis [19].

Conclusion

Our data allowed concluding that the application of a gel containing alginate capsules with silver ions to the periodontium of intact rats affected the intact periodontium in white rats, causing transient activation of blood flow. The latter lasted up to 24 hours after application and could be regarded as an irritation response. Loading TA into capsules contributed to neutralizing changes in perfusion and mechanisms of its modulation in the gums that occurred when the gel was applied to intact rats.

Application of a gel containing alginate capsules with silver ions to the affected area of the gums between days 14 and 21 of experimental periodontitis development permitted to partially correct inflammatory microcirculatory disorders in rats. Using a gel with microcapsules containing TA was more effective vs. gel without TA. The former corrected the disorders in perfusion, neurogenic tone of arterioles, myogenic tone of precapillary sphincters, as well as venous outflow in the microvasculature of the gums in rats with experimental periodontitis.

Therefore, TA loading reduces the irritating effect of alginate capsules with silver ions on the gums, and also improves the efficacy of correcting microcirculatory disorders in periodontitis, which experimentally substantiates the feasibility of using a targeted delivery system and extended release of TA in the gel for treating inflammatory periodontal diseases.

Conflict of interest: None declared.

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