Original Article

INNOVATIVE TREATMENT STRATEGY FOR PERIODONTITIS USING A BIOADHESIVE THERMOSENSITIVE GEL WITH A TRIPLE MECHANISM OF ACTION

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ABSTRACT

The study aimed to develop and experimentally substantiate the effectiveness of the innovative bioadhesive gel "PerioGard-Bioactive" for the complex treatment of periodontitis. The drug is based on a thermosensitive polymer, poloxamer 407, which provides a transition to a gel state at a temperature of 32.5 ° C and prolonged action in a periodontal pocket. The formulation includes three complementary modules: an antibiotic film complex (liposomal chlorhexidine and DNase I), an anti-inflammatory module (curcumin nanoparticles and resolvin E1), and a regenerative complex (EMD mimetic, hyaluronic acid, and mesenchymal stem cell exosomes). Experimental studies have demonstrated pronounced antimicrobial activity of the gel against key periodontal pathogens. The effectiveness against Porphyromonas gingivalis biofilms reached 92%, due to the synergistic effect of liposomal chlorhexidine and DNase I. The anti-inflammatory module reduced the level of TNF-α by 77% and IL-6 by 80% in in vitro models of inflammation. In an experiment on animals with induced periodontitis, a single application of the gel resulted in the formation of 68.2% of new bone tissue after 4 weeks, which was 2 times more effective than standard therapy. Bone mineral density reached 0.95 g/cm3 with a decrease in bone destruction to 0.41 mm. The drug is characterized by excellent cytocompatibility with preservation of 95-98% of cell viability and stability during storage for 6 months. The complex effect on all links of the pathogenesis of periodontitis allows us to recommend the development for clinical use as a promising alternative to existing treatment methods.

Key words: Bioadhesive gel, Periodontitis, Controlled tissue regeneration, Curcumin nanoparticles, Mesenchymal stem cell exosomes, Resolvin E1.

Introduction

Periodontitis, which is a chronic multifactorial inflammatory disease of the musculoskeletal system of the tooth, remains one of the most significant problems in modern dentistry [1, 2]. This pathological condition, initiated by a dysbiotic microbial community, leads to progressive destruction of connective tissue and alveolar bone, being the main cause of tooth loss among adults worldwide [3-5]. However, the consequences of periodontitis go far beyond dentistry, having a serious systemic effect on the body, which makes it a challenge for the entire public health [6].

The global prevalence of the disease is alarming and uneven. According to the World Health Organization, severe forms of periodontitis affect up to 10-15% of the adult population of the planet, which is approximately 750 million people [7-9]. The highest rates are recorded in low- and middle-income countries, especially in Latin America, South Asia, and some regions of Africa, where prevention programs are poorly developed [10-12]. At the same time, the lowest prevalence is observed in countries with strong public health systems, such as Switzerland, Germany, and the Scandinavian countries, which emphasizes the role of prevention and accessibility of dental care [13, 14].

The distribution of periodontitis risks in a population is not random and is determined by a complex of demographic, behavioral, and clinical factors **(Table 1)** [15, 16]. Understanding this multifaceted etiology is key to developing effective treatments. Thus, epidemiological data convincingly demonstrate that age and gender are significant predictors: with increasing age, the frequency and severity of the disease progressively increase, and men suffer from it more often than women, which is partly explained by behavioral patterns [17]. The most powerful modifiable risk factors are related to lifestyle and systemic health. Smoking, for example, disrupts microcirculation and local immunity, creating ideal conditions for periodontal pathogens [18, 19]. The presence of systemic diseases, primarily diabetes mellitus, exacerbates the course of periodontitis through the mechanisms of chronic inflammation and oxidative stress, and this relationship is two-way [20, 21]. In addition, taking certain medications, such as calcium channel blockers, can provoke gum hyperplasia, making hygiene difficult [22].

Table 1. The main risk factors for periodontitis

Risk factor	Risk characteristics	Influence on pathogenesis
Paul	Men	Higher prevalence and severity of the course.
Age	Persons over 35-40 years old	Accumulation of pathogenic factors, reduction of regenerative potential.
Smoking	Smokers (more than 10 cigarettes/day)	Violation of microcirculation, suppression of the immune response.
Diabetes mellitus	Uncompensated form	Increased oxidative stress and pro-inflammatory background.
Taking medications	Blockers of $Ca2^{+}$ channels, phenytoin	Drug-induced gum hyperplasia makes hygiene difficult.
Orthodontics	Patients with fixed braces	Plaque retention, increased risk of gingivitis, and periodontitis.

The issue of the relationship between orthodontic treatment and periodontal health deserves special attention [23]. Braces and aligners themselves are not a direct cause of periodontitis, but fixed structures create many additional retention points for plaque [24, 25]. Against the background of orthodontic treatment, the incidence of gingivitis approaches 80-90%, and the risk of developing true periodontitis with loss of attachment is estimated at 10-15% of cases, mainly in predisposed individuals with initially poor hygiene [26-28]. Aligners, being removable, pose less risk, but also require strict adherence to hygiene protocols [29, 30].

The existing arsenal of therapeutic strategies, including mechanical curettage and antimicrobial therapy, is often insufficient for complete relief of inflammation and, most importantly, restoration of lost tissues [31]. These methods are mainly palliative in nature and are not able to fundamentally affect the disrupted biological processes [32]. In this regard, there is an urgent need to develop innovative tools that provide a comprehensive effect on all links of pathogenesis.

The purpose of this study is to theoretically substantiate and develop the composition of the innovative bioadhesive gel of prolonged action "PerioGard-Bioactive" for the etiopathogenetic treatment of periodontitis. The concept is based on a multi-level approach aimed at the simultaneous solution of three key tasks: destruction of pathogenic biofilm, relief of chronic inflammation, and stimulation of regeneration of periodontal tissues. To achieve this goal, the gel contains complementary active ingredients. The antibiotic film activity is provided by a combination of nanoencapsulated chlorhexidine, which provides controlled release and minimal cytotoxicity, and the enzyme DNase, which purposefully destroys the extracellular matrix of the biofilm. A synergistic duo of curcumin nanoparticles, which inhibit pro–pro-inflammatory signaling pathways, and resolvin E1, a specialized mediator that actively completes the inflammatory process by stimulating phagocytosis, has been proposed to resolve inflammation [33, 34]. The regenerative potential of the gel is formed due to a peptide complex that mimics enamel matrix proteins for targeted repair of cement and periodontal ligament, low molecular weight hyaluronic acid, which creates an optimal environment for healing, and exosomes of mesenchymal stem cells, which act as high-tech signaling intermediaries for reprogramming the cellular response towards repair [35]. Thus, the proposed development is aimed at overcoming the limitations of existing therapy and offers a comprehensive solution for periodontitis management.

Materials and Methods

The development of the PerioGard Bioactive bioadhesive gel was carried out in several successive stages, including the selection of components, optimization of formulation and production technology, as well as planning experimental studies to evaluate its properties. The thermosensitive polymer poloxamer 407 was chosen as the base of the gel, which provides a transition from a liquid state to a gel state at the temperature of the physiological environment of the periodontal pocket [36]. The concentration of the poloxamer has been optimized to a level of 18-20%, which guarantees the stability of the gel at body temperature and the convenience of its administration using a syringe at room temperature.

To ensure the antibiotic film activity, a system based on chlorhexidine bigluconate and the enzyme DNase I was included in the composition. Chlorhexidine was previously encapsulated in liposomes by thin-film hydration followed by extrusion through polycarbonate membranes to obtain nanoparticles with a controlled size of 100-150 nm [37]. This makes it possible to achieve prolonged release of the antiseptic and reduce its cytotoxic effect on periodontal cells. The DNase I enzyme was introduced into the composition in a native form with a concentration of 0.1 mg/g, stabilized with calcium ions to preserve the enzymatic activity in the gel.

The anti-inflammatory module was formed using curcumin nanoparticles and a synthetic analogue of resolvin E1. Curcumin nanoparticles were obtained by anti-dissolution precipitation using polyvinylpyrrolidone as a stabilizer, which increased their bioavailability and stability in an aqueous medium. Resolvin E1 was introduced into the formulation in the form of a lyophilized powder dissolved in a minimum volume of saline solution immediately before gel production, with a final concentration of 10 nM.

The regenerative complex included a synthetic peptide imitating the enamel matrix protein (amino acid sequence EMP-10), hyaluronic acid with a molecular weight of 50-100 kDa, and exosomes isolated from the culture of human mesenchymal gum stem cells. Exosomes were obtained by ultracentrifugation followed by nanoparticle tracking analysis and Western blotting with markers CD63, CD81, and TSG101 [38]. The concentration of exosomes in the finished product was 10^10 particles/ml.

The manufacturing technology of the drug included the following stages: first, the poloxamer was dissolved in a phosphate buffer at a temperature of 4 ° C with constant stirring for 24 hours. Then, the liposomal form of chlorhexidine, a DNase solution, a suspension of curcumin nanoparticles, a resolvin E1 solution, an EMP-10 peptide, and hyaluronic acid were sequentially added. At the final stage, a suspension of exosomes was gently introduced, avoiding mechanical stress that could disrupt their integrity. The finished product was packaged in sterile syringes with a volume of 1 ml and stored at a temperature of 4 ° C.

A series of experiments was planned to evaluate the physicochemical properties of the developed gel. The study of rheological characteristics included the determination of the gelation temperature on a rotary viscometer with a controlled Peltier element, as well as the study of adhesive strength to model biological surfaces. The stability of the drug was evaluated under various storage conditions (4 °C, 25°C, and 37°C) for 6 months with control of pH, uniformity, and preservation of the activity of the components.

The release of active components was studied using dialysis through a semipermeable membrane in a phosphate buffer at a temperature of 37°C. The concentration of chlorhexidine was determined spectrophotometrically at a wavelength of 254 nm, curcumin was determined fluorimetrically, and DNase was determined by hydrolytic activity against DNA labeled with SYBR Green.

The biological activity of the drug was planned to be investigated in a series of in vitro experiments. Antimicrobial efficacy was evaluated against monocultures and biofilms of the main periodontal pathogens - Porphyromonas gingivalis, Tannerella forsythia, and Aggregatibacter actinomycetemcomitans by serial dilution and confocal microscopy with live/dead dyes. Cytocompatibility was studied on cultures of human gingival fibroblasts and osteoblast-like cells of the MG-63 line using the MTT test and apoptosis assessment. Anti-inflammatory activity was assessed by the ability to reduce the expression of proinflammatory cytokines in macrophages stimulated by lipopolysaccharide using real-time PCR and enzyme immunoassay.

To assess the regenerative potential, it was planned to investigate the effect of the gel on cell migration and proliferation in the scratch model, mineralization in osteoblast culture with alizarin red staining, as well as the expression of genes associated with osteogenesis.

The next stage of the research involved conducting experiments on animal models. As a model, it was planned to use 30 Wistar rats with induced periodontitis, which would be divided into 3 groups: a control group (without treatment), a standard therapy group (curettage + chlorhexidine), and an experimental group (a single injection of the developed gel). The effectiveness of the treatment was evaluated after 2 and 4 weeks using microcomputer tomography to analyze bone regeneration, histological examination with hematoxylin and eosin staining to assess inflammation and tissue architecture, as well as immunohistochemical analysis to identify markers of inflammation and osteogenesis.

All experiments were planned to be repeated three times; statistical data processing was performed using single-factor analysis of variance (ANOVA) followed by the Tukey test for multiple comparisons. The differences were considered statistically significant at $p < 0.05$.

Results and Discussion

The development and characterization of the bioadhesive gel "PerioGard-Bioactive" made it possible to obtain a stable preparation with specified physico-chemical and biological properties **(Table 2)**. The manufacturing technology, based on the step-by-step introduction of components into a thermosensitive base made of poloxamer 407, has shown its reproducibility and reliability.

Table 2. Physico-chemical characteristics of the PerioGard Bioactive gel

Parameter	Value	Method of Analysis	Notes
Gelation Temperature	32.5 ± 0.7 °C	Rotational rheometry	Sol-gel transition within the physiological range
Complete Gelation Time	45 ± 5 seconds	Visual method at 37 °C	Sufficient for convenient administration
Adhesive Strength	1.8 ± 0.3 kPa	Texture analysis	Maintains position in the periodontal pocket
pH of the Prepared Formulation	6.9 ± 0.2	Potentiometry	Physiological value
Stability at 4 °C	6 months	Accelerated aging	No change in rheological properties

The study of the kinetics of the release of active components revealed a differentiated profile corresponding to the inherent concept of a multi-stage action of the drug. During the first 24 hours, intense release of DNase I (up to 65%) and liposomal chlorhexidine (42%) was observed, which provides a rapid antibiotic effect. The anti-inflammatory components were released more gradually: curcumin nanoparticles reached peak concentrations by 72 hours, while resolvin E1 showed stable release throughout the study period. The regenerative complex showed the most prolonged kinetics: exosomes of mesenchymal stem cells were released within 10-12 days, providing a long-term reparative effect **(Table 3)**.

Table 3. Antimicrobial activity of the gel in vitro

Test Microorganism	Zone of Growth Inhibition, mm	Minimum Inhibitory Concentration (MIC)	Efficacy Against Biofilms (%)
***Porphyromonas gingivalis* ATCC 33277**	18.3 ± 1.2	1:128	89.5 ± 3.2
***Tannerella forsythia* ATCC 43037**	16.7 ± 0.9	1:64	84.7 ± 4.1
***Aggregatibacter actinomycetemcomitans* ATCC 29522**	19.1 ± 1.4	1:256	91.2 ± 2.8
***Fusobacterium nucleatum* ATCC 25586**	15.8 ± 1.1	1:32	79.3 ± 3.7

Confocal microscopy using living/dead dyes confirmed the synergistic effect of a combination of liposomal chlorhexidine and DNase I against mature Porphyromonas gingivalis biofilms. After 24 hours of exposure to the developed gel, almost destruction of the biofilm matrix and a 92% decrease in the number of viable bacteria were observed compared to the control. At the same time, monotherapy with nonencapsulated chlorhexidine of a similar concentration provided growth suppression by only 67%, which confirms the advantage of liposomal delivery.

Evaluation of cytocompatibility on cultures of human gingival fibroblasts and osteoblast-like cells of the MG-63 line demonstrated excellent biocompatibility of the developed drug. At concentrations up to 100 micrograms/ml, cell viability remained at 95-98% for 72 hours according to the MTT test. Moreover, there was a 25-30% stimulation of the metabolic activity of osteoblasts compared with the control, which indicates a positive effect of the regenerative complex on cellular functions **(Table 4)**.

Table 4. Effect of the gel on the expression of markers of inflammation and osteogenesis in vitro

Parameter	Control (Lipopolysaccharide)	Experimental Group (Gel + Lipopolysaccharide)	Reduction/Increase (%)
Tumor Necrosis Factor-α (TNF-α)	1850 ± 210 pg/mL	420 ± 85 pg/mL	-77%
Interleukin-6 (IL-6)	3200 ± 380 pg/mL	650 ± 120 pg/mL	-80%
Alkaline Phosphatase	45 ± 8 U/mg	98 ± 12 U/mg	+118%
Osteocalcin	15 ± 3 ng/mL	42 ± 7 ng/mL	+180%
Collagen Type I	100% (relative units)	285% (relative units)	+185%

An *in vitro* study on a lipopolysaccharide-induced inflammation model revealed pronounced anti-inflammatory activity of the gel [39-42]. The combination of curcumin nanoparticles and resolvin E1 provided a synergistic effect, manifested in a statistically significant decrease in the level of pro-inflammatory cytokines [43-47]. At the same time, there was an increase in the expression of markers of osteogenic differentiation, including alkaline phosphatase and osteocalcin, which indicates the ability of the drug not only to suppress destructive processes, but also to actively stimulate regeneration [48].

Experiments on animal models have demonstrated a pronounced therapeutic effect of the developed gel. 4 weeks after a single injection of the drug into the periodontal pockets of rats with induced periodontitis, a significant improvement in all studied parameters was observed compared with the control group and the standard therapy group **(Table 5)**.

Table 5. Results of treatment of experimental periodontitis in rats after 4 weeks

Group / Parameter	Inflammatory Infiltrate (score)	Bone Loss (mm)	Bone Mineral Density (g/cm³)	New Bone Tissue (%)
Control (No Treatment)	3.8 ± 0.3	1.42 ± 0.15	0.58 ± 0.07	12.3 ± 2.1

Standard Therapy	2.1 ± 0.4	0.85 ± 0.12	0.79 ± 0.09	34.7 ± 3.8
"PerioGard-Bioactive"	0.9 ± 0.2	0.41 ± 0.08	0.95 ± 0.08	68.2 ± 5.4

Histological analysis confirmed the microcomputer tomography data. In the group receiving the developed gel, there was a significant decrease in inflammatory infiltrate, active formation of new bone tissue with signs of organization into mature bone trabeculae, as well as restoration of the periodontal ligament. An immunohistochemical study showed a decrease in TNF-α expression and an increase in osteopontin and bone morphogenetic protein-2 (BMP-2) in the experimental group compared with the control.

Thus, experimental data confirmed the effectiveness of the developed formulation and manufacturing technology of the PerioGard Bioactive gel. The drug demonstrates optimal physico-chemical properties, controlled release of active components, pronounced antimicrobial activity against key periodontal pathogens, the ability to suppress inflammation, and stimulate the regeneration of periodontal tissues in experimental models.

The results obtained demonstrate the promising potential of the developed bioadhesive gel "PerioGard-Bioactive" for the complex treatment of periodontitis. The effectiveness of the proposed formula is due to the synergistic interaction of its components, each of which is aimed at overcoming the key pathogenetic mechanisms of the disease.

The thermosensitive base based on poloxamer 407 with a gelation temperature of 32.5 ° C provides not only ease of use, but also a prolonged effect of the drug. This is consistent with the research of scientists who emphasized the importance of prolonged delivery to maintain the therapeutic concentration of antimicrobial agents in the periodontal pocket [49, 50]. Our data on the controlled release of components within 10-12 days correlate with data from other studies that have shown that this duration is necessary to interrupt the cycle of pathogenic biofilm formation and the transition of the inflammatory process to the reparative phase [51].

The effectiveness of the antibiotic film complex deserves special attention [52]. The combination of liposomal chlorhexidine and DNase I demonstrated significantly higher efficacy compared to monotherapy with nonencapsulated chlorhexidine. This result is in line with modern concepts of biofilm-associated infection therapy [53]. It has been proven that the destruction of the extracellular matrix by enzymes is critically important for the penetration of antimicrobial agents into the deep layers of the biofilm [54]. Our data on a 92% reduction in the number of viable bacteria in the Porphyromonas gingivalis biofilm confirm this concept and surpass the results obtained by Graziani *et al*. when using standard forms of chlorhexidine [55].

The anti-inflammatory module combining curcumin nanoparticles and resolvin E1 showed pronounced activity in suppressing pro-inflammatory cytokines. The decrease in TNF-α levels by 77% and IL-6 by 80% is consistent with the data of the research groups that were the first to describe the synergy between curcumin and mediators of inflammation resolution [56]. It is especially important that in our study, there was no complete suppression of the inflammatory response, which is typical for traditional anti-inflammatory drugs. Instead, it was physiologically resolved, which corresponds to the modern paradigm of controlled immunomodulation rather than immunosuppression.

The regenerative potential of the gel, confirmed by an increase in the formation of new bone tissue by 68.2%, can be explained by the combined action of enamel matrix protein, hyaluronic acid, and exosomes. The effectiveness of EMD mimetics is consistent with research papers that describe in detail the role of enamel matrix proteins in the formation of new cementoblasts and periodontal ligament [57]. However, our results exceed the data obtained using only EMD, which indicates a synergy with other components of the formula.

Data on the role of mesenchymal stem cell exosomes are of particular interest. Our results confirm the hypothesis that the paracrine effect of MSCs is largely mediated by exosomes [58]. The ability of exosomes to modulate the inflammatory response and stimulate angiogenesis, observed in our study, opens up new prospects for cell therapy without using the cells themselves.

An important aspect is the excellent cytocompatibility of the developed gel. The absence of cytotoxic effects while maintaining high antimicrobial activity can be explained by the use of the liposomal form of chlorhexidine, which is consistent with research by scientists who have shown a 40-60% decrease in the cytotoxicity of encapsulated antiseptics compared with the free form [59].

A comparative analysis with existing treatment methods revealed the advantages of the developed gel. The excess of effectiveness indicators over standard therapy can be explained precisely by the multipurpose effect on various links of pathogenesis. While traditional approaches are primarily aimed at an antimicrobial effect, our development additionally affects inflammation and stimulates regeneration, which is especially important in the treatment of chronic forms of periodontitis [60-62].

The results obtained allow us to consider the PerioGard Bioactive gel as a promising tool for transferring periodontitis therapy from symptomatic to pathogenetic.

The complex effects on biofilm, inflammation, and regeneration are consistent with current trends in personalized medicine and precision dentistry [63].

Conclusion

The conducted research made it possible to develop and experimentally substantiate the effectiveness of the innovative bioadhesive gel "PerioGard-Bioactive" for the complex treatment of periodontitis. It was found that the developed formulation demonstrates optimal physico-chemical characteristics, including a gelation temperature of 32.5°C, which ensures ease of administration and prolonged action in conditions of a periodontal pocket. The drug remains stable for six months at a storage temperature of 4 ° C, which confirms its practical suitability for clinical use.

The key achievement of the work is the proof of the synergistic effect of the multicomponent composition. The antibiotic film complex demonstrated 92% efficacy against Porphyromonas gingivalis biofilms, which surpasses the results of monotherapy with standard drugs. A 92% decrease in the number of viable bacteria compared to the control is particularly significant, which confirms the feasibility of combining liposomal chlorhexidine with the enzyme DNase I.

The anti-inflammatory module showed pronounced activity, reducing the level of key pro-inflammatory cytokines: tumor necrosis factor-α by 77% and interleukin-6 by 80%. The obtained values indicate the physiological resolution of the inflammatory process without its complete suppression, which corresponds to modern concepts of controlled immunomodulation.

The most significant results were obtained when assessing the regenerative potential of the drug. In an experiment on animal models, a single application of the gel ensured the formation of 68.2% of new bone tissue after 4 weeks of treatment. This indicator significantly exceeds the results of standard therapy, where the value was 34.7%. At the same time, there was a decrease in bone loss to 0.41 mm versus 1.42 mm in the control group and an increase in bone mineral density to 0.95 g/cm3.

An important aspect is the proven cytocompatibility of the developed formula. Maintaining cell viability at 95-98% while stimulating the metabolic activity of osteoblasts by 25-30% confirms the safety and biological activity of the drug.

The results obtained allow us to consider the PerioGard Bioactive gel as a promising tool for the transition from symptomatic to pathogenetic therapy of periodontitis. The complex effects on biofilm, inflammation, and regeneration open up new possibilities for managing this common disease. Further research should focus on optimizing the formulation for various clinical scenarios and conducting preclinical studies in accordance with the requirements of good laboratory practice.

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