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SUBSTANTIATION OF MANUFACTURING TECHNOLOGY AND CLINICAL APPLICATION OF PERIODONTAL GEL COMPOSITION BASED ON PHYTOPREPARATION WITH ANTIOXIDANT PROPERTIES IN THE TREATMENT OF PERIODONTAL DISEASES IN ORTHODONTIC PATIENTS

Actuality. *In order to prepare patients with dentoalveolar anomalies (DA) against the background of gingivitis and periodontitis for active orthodontic treatment in order to reduce oxidative stress, it is advisable to use herbal remedies with antioxidant properties and*

non-steroidal anti-inflammatory drugs that have anti-inflammatory, antimicrobial, analgesic, anti-edematous effects and accelerate reparative processes.

***The purpose** is to develop and clinically test an extemporaneous periodontal gel composition based on a plant-derived flavonoid complex and benzydamine hydrochloride for the treatment of patients with malocclusion in the presence of gingivitis and generalized periodontitis before and during the active phase of orthodontic treatment.*

***Material and methods.** The development of the gel composition involved the creation of six batches containing different combinations of the intended main components. The optimum concentration of the gel-forming agent was selected experimentally. A comparative characterization of the number of components in these six series, depending on the concentration of the gelator, was carried out and the selection of active and auxiliary components of the gel composition was substantiated. The study examined 30 orthodontic patients aged 18 to 30 years with DA and periodontal tissue diseases, who were divided into two equal groups of 15 people. The main group received treatment with the developed gel composition, and the comparison group received a traditional treatment regimen. The observation periods using the OHI-S index, Mühlemann H.R. bleeding index and PMA were performed immediately after treatment in 5, 10 days and after one, six and 12 months of active orthodontic treatment with braces.*

***Research results.** After the experimental establishment of the final composition of the gel composition containing sodium alginate, nipagine, water for injection, benzydamine and comb drug based on flavonoids, its clinical testing was carried out. The analysis of the dynamics of the applied clinical and instrumental methods in patients of the main group who underwent treatment with the developed gel composition at different periods of observation showed better statistically significant values in contrast to those of the comparison group.*

***Conclusion.** The clinical results obtained allow us to characterize the gel composition proposed for the treatment of periodontal tissue diseases in orthodontic patients as a pathogenetically sound and highly effective agent that allows optimizing and accelerating healing processes, has intense anti-inflammatory properties and no side effects.*

***Key words:** periodontal disease, treatment, gel composition, herbal flavonoids, orthodontic patients.*

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ОБҐРУНТУВАННЯ ТЕХНОЛОГІЇ ВИГОТОВЛЕННЯ ТА КЛІНІЧНЕ ЗАСТОСУВАННЯ ПАРОДОНТАЛЬНОЇ ГЕЛЕВОЇ КОМПОЗИЦІЇ НА ОСНОВІ ФІТОПРЕПАРАТУ З АНТИОКСИДАНТНИМИ ВЛАСТИВОСТЯМИ В ЛІКУВАННІ ЗАХВОРЮВАНЬ ПАРОДОНТА В ОРТОДОНТИЧНИХ ПАЦІЄНТІВ

Актуальність. *Для підготовки пацієнтів із зубощелепними аномаліями (ЗЩА) на тлі гінгівіту та пародонтиту до активного ортодонтичного лікування з метою зниження оксидативного стресу доцільним є застосування фітопрепаратів з антиоксидантними властивостями та нестероїдних протизапальних засобів, які виявляють протизапальну, протимікробну, знеболювальну, протинабрякову дію та прискорюють репаративні процеси.*

Мета роботи *– розроблення та клінічна апробація екстемпоральної пародонтальної гелевої композиції на основі флавоноїдного комплексу рослинного походження та бензидаміну гідрохлориду для лікування пацієнтів із ЗЩА на тлі гінгівіту і генералізованого пародонтиту до та в процесі активного періоду ортодонтичного лікування.*

Матеріали та методи. *Розроблення гелевої композиції передбачало створення шести серій, які містили різні комбінації, з основних компонентів. Експериментальним шляхом проводили вибір оптимальної концентрації гелеутворювача. Проведено порівняльну характеристику кількості компонентів у зазначених шести серіях залежно від концентрації гелеутворювача та обґрунтовано підбір активних і допоміжних компонентів гелевої композиції. Обстежено 30 ортодонтичних пацієнтів віком від 18 до 30 років із ЗЩА та захворюваннями тканин пародонта, яких розділили на дві рівноцінні групи по 15 осіб. Основна група отримувала лікування розробленою гелевою композицією, а група порівняння – традиційну схему лікування. Терміни спостереження з використанням індексу OHI-S, індексів кровоточивості за Mühlemann H.R. та PMA проводили безпосередньо після лікування через 5, 10 днів та через один, шість та 12 місяців активного періоду ортодонтичного лікування незнімною брекет-технікою.*

Результати дослідження. *Після експериментального встановлення остаточного складу гелевої композиції, що містила альгінат натрію, ніпагін, воду для ін'єкцій, benzydamine та comb drug на основі флавоноїдів, було проведено її клінічну апробацію. Аналіз динаміки застосованих клінічно-інструментальних методів у пацієнтів основної групи, що пройшли курс лікування з розробленою гелевою композицією, на різних термінах спостереження демонстрували кращі, статистично достовірні значення на противагу показникам групи порівняння.*

Висновки. *Отримані клінічні результати дозволяють схарактеризувати запропоновану для лікування захворювань тканин пародонта в ортодонтичних пацієнтів гелеву композицію як патогенетично обґрунтований та високоефективний засіб, що дозволяє оптимізувати та пришвидшити процеси загоєння, має інтенсивні протизапальні властивості та відсутність побічних ефектів.*

Ключові слова: *захворювання пародонту, лікування, гелева композиція, рослинні флавоноїди, ортодонтичні пацієнти.*

Actuality. Aseptic inflammation in periodontal tissues is a source of reactive oxygen species in the oral cavity and is closely related to oxidative stress (OS). In patients with dentoalveolar anomalies (DA) prone to periodontal disease, during the active period of orthodontic treatment, OS provokes the release of inflammatory mediators (cytokines) after mechanical impact on the teeth and causes a cascade of reactions leading to bone remodeling of the alveolar processes of the jaws and tooth movement (Erbe, et al., 2023). It has been established that treatment with fixed orthodontic appliances can affect the composition, accumulation and increased virulence of periodontopathogenic subgingival microbiota. This leads to inflammation in the gingival tissues, which manifests itself in the form of edema and bleeding during probing in patients with significantly decreased level of individual oral hygiene, which in turn deepens inflammatory and destructive processes in periodontal tissues (Papageorgiou, et al., 2018; Cerroni, et al., 2018).

In order to prepare patients with DA against the background of gingivitis and periodontitis for active orthodontic treatment in order to reduce OS, it is advisable to use herbal remedies with antioxidant properties and non-steroidal anti-inflammatory drugs. Medicinal prod-

ucts belonging to these groups effectively act in conditions of OS and hypoxia caused by inflammatory processes and stress-modulating effects of fixed orthodontic appliances, inhibit peroxides and intermediate products of lipid free radical oxidation, have anti-inflammatory, antimicrobial, analgesic and decongestant effects, and accelerate reparative processes. A literature search revealed numerous evidences that herbal components with their biological properties are the most commonly used medicinal agents in periodontal therapy (Adamczyk, et al., 2022; Mooney, et al., 2021), in particular for orthodontic patients (Talpos Niculescu et al., 2024).

Considering the fact that the main periodontopathogens rapidly develop resistant strains to classical antibiotics, modern research aims to formulate alternative approaches to combat them using herbal preparations with anti-inflammatory, antibacterial, antioxidant, and other properties. It has been proven that flavonoids, as free radical scavengers, exhibit pronounced antioxidant, anti-inflammatory, antiallergic, antiviral, antibacterial, antiaggregant, and antitumor effects (Gutiérrez-Venegas, et al., 2019). They are widely used in general medicine and dentistry for the treatment of oral cavity diseases, protecting cells from damage and blood vessels from rupture, and preventing inflammation in various tissues and organs (Abou Baker, 2022; Fernández-Rojas, & Gutiérrez-Venegas, 2018). The phenolic structure allows the molecules of these substances to interact with free radicals, resulting in a decrease in the intensity of lipid peroxidation (LPO) and inhibition of the formation of the main negative factor – malondialdehyde (Fernández-Rojas, & Gutiérrez-Venegas, 2018).

The aim of this study was to develop and clinically test an extemporaneous periodontal gel composition based on a plant-derived flavonoid complex and benzydamine hydrochloride for the treatment of patients with malocclusion in the presence of gingivitis and generalized periodontitis before and during the active phase of orthodontic treatment.

Materials and methods. At the beginning of the study, six series of gel compositions were created containing different combinations of the anticipated main components: 1) benzydamine solution, 100 ml of which contains 0.15 g of benzydamine hydrochloride (BH); 2) crushed tablet form of benzydamine; 3) comb drug drops containing plant flavonoids – extracts from *Deschampsia caespitosa* and *Agrostis capillaris*; 4) for the gel base – sodium alginate, nipagin (methylparaben), and water for injection. At the first stage of the gel composition formulation, the optimal concentration of the gelling agent was selected experimentally. A comparative analysis of the component quantities in the six series was also performed, depending on the concentration of the gelling agent, and the selection of active and auxiliary components was justified.

A total of 30 orthodontic patients aged 18 to 30 years of both sexes with malocclusion and periodontal tissue diseases were examined. To diagnose periodontal diseases, we used the classification of diseases and conditions of periodontal and peri-implant tissues (EFP & AAP World Workshop, 2017), (Caton, et al., 2018). Gingivitis associated with dental biofilm was diagnosed in 14 patients. In 8 patients, gingivitis was mediated by potential modifying risk factors, and in another 8 patients, generalized periodontitis stage I–II, grade A, was diagnosed. A comprehensive clinical and instrumental examination was conducted to determine index indicators characterizing the condition of periodontal tissues: the oral hygiene index OHI-S (Green J.C., Vermillion J.R., 1964), bleeding index according to Mühlemann H.R. as modified by Cowell R. et al., 1975, and the PMA index (Parma, 1960) for gingival inflammation (Newman, et al., 2019).

All patients were randomly divided into two groups. The main group included 15 patients (11 with gingivitis and 4 with generalized periodontitis stage I–II, grade A), and the comparison group included 15 patients with similar diagnoses.

In the main group, the treatment method involved intraoral scanning of the oral cavity using the 3Shape TRIOS 3 Pod Basic scanner (3Shape, Denmark) before and after the installation of fixed orthodontic appliances to create digital impressions for analysis and processing. Models were printed using the Phrozen Sonic 4K 2022 3D printer (Phrozen, Taiwan). Individual trays (for upper and lower jaws) were fabricated in the dental laboratory using the MINISTAR S® device (SCHEU-DENTAL GmbH, Germany), providing reservoir areas for the prolonged action of the developed extemporaneous periodontal gel composition, patented under the name «Benzidaflaziverdin» (PGCB) (Hodovanyi, et al., 2022). Depending on the clinical situation, patients wore the PGCB-filled tray for 2 hours once daily. The treatment course consisted of five applications following initial periodontal therapy, which included professional hygiene and the Scaling & Root Planing (SRP) protocol as indicated.

Patients in the comparison group received traditional treatment following the International Clinical Protocols of Duodecim Medical Publications Ltd, particularly guideline 00163. This protocol was supplemented with a dental gel based on choline salicylate and cetalkonium chloride, applied to the gingival mucosa using a spatula in the form of applications. Patients were advised not to

rinse their mouth or eat for 30 minutes after application. The course of treatment lasted 5 days.

Individual hygiene monitoring and clinical examinations, including index evaluations, were performed immediately after treatment, on days 5 and 10, and at 1, 6, and 12 months during the active phase of fixed orthodontic treatment.

Bioethics. The study was performed taking into account the main provisions of the GCP ICH and the Declaration of Helsinki on biomedical research where a person is the object, and the subsequent revision, Seoul, 2008; the Council of European Convention on Human Rights and Biomedicine (2007) and the recommendations of the Bioethics Committee at the Presidium of the National Academy of Medical Sciences of Ukraine (2002), as well as a positive opinion of the commission on ethics of Danylo Halytsky Lviv National Medical University (extract from protocol No. 1 of January 15, 2024). No violations of moral and ethical norms were identified during the research.

Statistical analysis. The obtained numerical data were analyzed using commonly accepted statistical methods. The creation and editing of the primary database were performed in Microsoft Excel. Statistical processing was carried out using the STATISTICA 6.0 software package for biomedical research. Variation analysis methods included the calculation of the arithmetic mean (M), standard error (±m), standard deviation (σ), and significance of differences (p-value). The degree of reliability (p) of the obtained results was determined using the Student's t-test. Results were considered statistically significant at $p<0.05$ and highly significant at $p<0.01$ (Welsby, & Weatherall, 2022).

Results and discussion. The proposed ratio of excipients in the development of PGCB was optimal and provided the necessary therapeutic effect, thanks to the experimental determination of drug dosages by creating six series of gel compositions containing different combinations of active and auxiliary components (table 1).

To create a structural base that would ensure a convenient shape, stability and delivery of the active ingredients of the periodontal gel composition, a gel base was first created. The following excipients were used for this purpose:

– gel-forming agent – sodium alginate, responsible for viscosity and consistency;

– preservative – nipagine (methyl paraben), to avoid microbial contamination;

– solvent – purified water as the main component in which the gelling agent and preservative dissolve, and also promotes the swelling of the gelling agent.

Rationale for selection and calculation of sodium alginate concentration.

When developing the gel composition, sodium alginate was chosen as a gelling agent. Since it is an environmentally friendly gelling agent, hypoallergenic, and has the ability to form gels, it meets the requirements for dental gel bases. Sodium alginate is practically harmless, not absorbed into the bloodstream, and well tolerated by the body, so this compound is recommended by the WHO and FDA as an excipient in pharmaceuticals and as a food additive. Taking into account all these properties of sodium alginate, we have chosen it as a promising, non-toxic, safe gelator with good adhesion for the development of a periodontal gel composition based on a herbal preparation with antioxidant properties for the treatment of orthodontic patients with periodontal diseases.

To determine the optimal concentration of the gelling agent, three samples were experimentally prepared across six series using sodium alginate concentrations of 1%, 5%, and 10%. The calculations for the gel compositions are presented in table 2. Visual assessment revealed that the gel base with 1% sodium alginate had a consistency that was too fluid and runny. In contrast, the 10% concentration resulted in a gel that was overly thick, uneven in texture, lumpy, and lacked plasticity. In both cases, these properties prevented the proper application and fixation of the gel composition to the gingival tissue. As a result, the 5% sodium alginate concentration was determined to be optimal for the formulation of the gel base.

Table 1

Experimental determination of drug combinations in the development of PGCB

Series	Composition	Drug Combinations
Series 1	Gel base	sodium alginate + nipagin + water
Series 2	Gel with BH	Gel base + benzydamine solution
Series 3	Gel with BH	Gel base + benzydamine powder
Series 4	Gel with BH	Gel base + benzydamine solution + benzydamine powder
Series 5	Gel with comb drug based on flavonoids	Gel base + comb drug containing flavonoids
Series 6	Gel with BH + comb drug based on flavonoids	Gel base + benzydamine solution + benzydamine powder + comb drug containing flavonoids

Table 2

Comparative characteristics of the component quantities in six series of experimental gel compositions depending on the concentration of the gelling agent

№	Substance name	Series 1	Series 2	Series 3	Series 4	Series 5	Series 6
Gelling agent – sodium alginate 10%							
1	sodium alginate	1,0	1,0	1,0	1,0	1,0	1,0
2	nipagin	0,01	0,01	0,01	0,01	0,01	0,01
3	benzydamine solution, 0,15 %	–	2 ml	–	1 ml	–	1ml
4	benzydamine, tab.	–	–	0,73	0,365	–	0,365
5	comb drug based on flavonoids, drops	–	–	–	–	1,5 мл	1,5 мл
6	water for injections	to 10,0	to 10,0	to 10,0	to 10,0	to 10,0	to 10,0
Gelling agent – sodium alginate 5%							
1	sodium alginate	0,5	0,5	0,5	0,5	0,5	0,5
2	nipagin	0,01	0,01	0,01	0,01	0,01	0,01
3	benzydamine solution, 0,15 %	–	2 ml	–	1 ml	–	1 ml
4	benzydamine, tab.	–	–	0,73	0,365	–	0,365
5	comb drug based on flavonoids, drops	–	–	–	–	1,5 ml	1,5 ml
6	water for injections	to 10,0	to 10,0	to 10,0	to 10,0	to 10,0	to 10,0
–	–	9,5 ml	7,5 ml	8,7 ml	8,1 ml	8 ml	6,6 ml
Gelling agent – sodium alginate 1%							
1	sodium alginate	0,1	0,1	0,1	0,1	0,1	0,1
2	nipagin	0,01	0,01	0,01	0,01	0,01	0,01
3	benzydamine solution, 0,15 %	–	2 ml	–	1 ml	–	1ml
4	benzydamine, tab.	–	–	0,73	0,365	–	0,365
5	comb drug based on flavonoids, drops	–	–	–	–	1,5 ml	1,5 ml
6	water for injections	to 10,0	to 10,0	to 10,0	to 10,0	to 10,0	to 10,0
–	–	9,89 ml	7,89 ml	9,16 ml	8,53 ml	8,34 ml	7,03 ml

Justification for the Selection of benzydamine and comb drug concentration.

In the development of the pharmaceutical composition, finished medicinal products (DMPs) were used as active substances, rather than the corresponding substances. This choice is due to the fact that when developing a gel pharmaceutical composition, the substance benzidamine is a medicinal product that has various legal restrictions. In Ukraine, ready-made dosage forms (sprays, tablets, solutions) with benzidamine are available over the counter. In order to study the market of substances in Ukraine, we analyzed the availability of registered substances of Benzydamine hydrochloride in the State Register of Medicines. As a result of the analysis, 6 registered substances of benzidamine hydrochloride were obtained. The results showed that the applicants of this substance are the following Ukrainian pharmaceutical companies: "Darnytsa", "Vertex", "Farmak" and "Sperko Ukraine". The vast majority of these substances are manufactured in India. The pharmaceutical substance benzidamine, i.e. powder for the manufacture of medicines, is controlled by the State Administration on Medicines and its sale to individuals is limited, as such substances are intended mainly for pharmaceutical production or pharmacies that manufacture prescription drugs. That is, it is difficult or impossible for a doctor, dentist or pharmacist to purchase benzidamine as an individual due to legal restrictions. That is why we chose a finished drug product based on the active ingredient benzidamine hydrochloride, rather than a substance.

In addition, to develop a gel composition based on a herbal product with antioxidant properties, drops of liquid extract from the herb Pike's Foot and the herb Voynich's Foot with a flavonoid content of at least 0.32 mg/ml were selected in the dosage form. This herbal medicine is a domestic product, unique and the only one on the Ukrainian market. For the development of the gel composition, the finished drug was chosen, since the difference between the finished drug and the substance is only in the volume of the container: glass vials of 10 ml,

or 30 ml, or 50 ml and In bulk containers: 20 l, 30 l in plastic canisters. Since small volumes of herbal medicine are required for experimental development, manufacturing and use in clinical practice, we used a finished drug rather than a substance to save money on the purchase of a gel composition carrier.

Justification for the selection of BH.

Considering that even with the use of individual trays for periodontal dressings, there is direct contact of PGCB with damaged gingival areas and the potential for the agent to enter the oral fluid with a possibility of ingestion, an optimal and permissible dose of BH suitable for oral administration was selected.

For comparative purposes, the following pharmaceutical forms of benzydamine were used: an oral rinse solution and lozenges for resorption. According to the manufacturer's instructions, one dose of a benzydamine lozenge (1 tablet) is equivalent to 3 mg of BH. This dosage (3 mg) per one procedure with the periodontal dressing was taken as the basis for PGCB formulation.

Thus, the optimal and permissible dose of BH for PGCB is 3 mg per procedure, based on the approved dosage of the benzydamine lozenge.

According to the instructions, one dose of benzydamine oral solution equals one measuring cup (15 ml of 0.15% solution), which corresponds to 22.5 mg of BH.

0.15 g – 100 ml of solution	X = 0.0225 g = 22.5 mg BH
X g – 15 ml of solution	contained in 15 ml of solution

To determine how much ml of benzydamine 0.15% solution is needed to obtain a dosage of 3 mg of BH, a mathematical calculation was performed using the proportion:

15 ml of solution – 22.5 mg	X = 2 ml of benzydamine 0,15% solution
X ml of solution – 3 mg	–

Rationale for choosing the comb drug concentration.

According to the comb drug instruction, it is possible to apply topical drops to the mucous membranes in the amount of 1.5 ml of comb drug in the form of a prepared solution. These data were used as the basis for selecting the optimal permitted dose for 1 procedure, and the content of comb drug in the amount of 1.5 ml was chosen for the manufacture of 10 g of gel.

Rationale for choosing the concentration of nipagine.

In the manufacture of the gel base, nipagine was chosen as a preservative at a concentration of 0.1%. Nipagine is also included in the finished drug (benzidamine hydrochloride – oral solution 1.5 mg/ml) in an amount of 1 mg/ml, i.e., a concentration of 0.1%. Given this, it was considered appropriate to add an additional 0.1% concentration of nipagine to the gel composition. The total concentration of nipagine is within the permissible limits of up to 0.2%. The expediency of the additional introduction lies in the fact that in the manufacture of the gel composition, we previously made a gel base for which a longer storage was expected.

Since it took 10-12 hours for the sodium alginate gel-forming agent to swell and dissolve, we made a large volume of the gel composition, the base, which was stored at room temperature in a plastic container with a tightly screwed lid and was intended for reuse and long-term storage. For this purpose, nipagine was used in a concentration of 0.1% for the gel base, which was already mixed extemporaneously with the active ingredients immediately before the procedure of applying the dressing (mouthguard) during the patient's visit.

The specifics of the technological process of manufacturing PGCB are presented in table 3.

The following visual results were obtained:

– **Series 1**: Transparent gel, viscous, with bubbles, non-flowing.

– **Series 2**: Transparent gel, slightly pale greenish tint, viscous.

– **Series 3**: Milky-green gel, homogeneous mass, no lumps, non-flowing, holds its shape.

Table 3

Comparative characteristics of the number of components in six series of gel compositions

№	Substance name	Series 1	Series 2	Series 3	Series 4	Series 5	Series 6
1	sodium alginate	0,5	0,5	0,5	0,5	0,5	0,5
2	Nipagin	0,01	0,01	0,01	0,01	0,01	0,01
3	benzydamine solution, 0,15 %	-	2 ml	-	1 ml	-	1 ml
4	benzydamine, tab.	-	-	0,73	0,365	-	0,365
5	comb drug based on flavonoids, drops	-	-	-	-	1,5 ml	1,5 ml
6	water for injections	to 10,0	to 10,0	to 10,0	to 10,0	to 10,0	to 10,0
-		9,5 ml	7,5 ml	8,7 ml	8,1 ml	8 ml	6,6 ml

– **Series 4**: Milky-green gel without bubbles, no lumps.

– **Series 5**: Yellowish-brown-green gel, lump formation observed.

– **Series 6**: Emerald-green gel with barely noticeable lumps, non-flowing, holds its shape, and was selected as the final variant.

The final version (**Series 6**) of the product in the form of an extemporaneous periodontal gel composition was established with the following ratio of components: sodium alginate 0.5; nipagine 0.01; benzydamine solution 0.15% 1 ml; benzydamine tablet 0.365, comb drug based on flavonoids, drops 1.5 ml; water for injection up to 10.0.

Thus, series 6 is a gel composition containing a gel base, comb drug and benzydamine in two dosage forms: tablet and liquid, in the form of a solution for rinsing the mouth. When calculating the quantitative ratio of benzydamine, half of the dose of each dosage form was recalculated to avoid exceeding and doubling the permissible therapeutic dose of benzydamine. The optimal permitted dose of benzydamine is 3 mg per treatment, which is contained in 1 benzydamine tablet weighing 0.73 g.

Accordingly, ½ dose is 1.5 mg = 0.0015 g of the active ingredient benzydamine.

½ dose of the tablet form = 0.73 g : 2 = 0.365 g of benzydamine tablets

½ liquid form (solution) = 1 ml of 0.15% benzydamine solution

We realize that using these two dosage forms increases the amount of excipients in the gel formulation we have developed. However, it is thanks to this unique combination and the used components of the finished medicinal products that we managed to achieve the desired consistency to ensure adhesion (adhesion to the oral mucosa), reduce spreading and swallowing of the gel, and keep it clearly in the affected area of the gums. This is especially important for the prolonged and effective action of the gel composition in orthodontic patients with periodontal disease.

Sodium alginate and nipagin were weighed, mixed with water for injection, and left for 10–12 hours for dissolution and swelling. Benzydamine tablets were weighed, ground in a mortar, and the resulting powder was thoroughly mixed with the gel base. Comb drug based on flavonoids was added to the composition and thoroughly mixed. The resulting composition has an intense emerald-green color, homogeneous soft-plastic consistency, holds its shape well, and is convenient for application both directly to the gums and in an individual molded cap. The advantage of the proposed treatment is its accessibility, simplicity of execution, and convenient form for use.

Clinical observations showed that the assessment of the hygienic condition of the oral cavity in orthodontic patients with periodontal diseases in both study groups before treatment demonstrated a low level of individual hygiene and high indicators of the corresponding indices, with no significant difference between the groups. In the main group, the OHI-S index was 2.58±0.19 points, while in the comparison group, the average values were 2.49±0.20 points. These values fully corresponded to unsatisfactory individual oral hygiene. Objective signs of inflammation were recorded: gum swelling, hyperemia with a cyanotic tint, bleeding, and pain upon palpation. The PMA and bleeding indices according to Mühlemann H.R. before treatment in the main group were 36.59±1.17% and 1.38±0.17 points, respectively, while in the comparison group, the indices were 37.32±1.83% and 1.27±0.24 points, which corresponded to the course of moderate inflammation.

Analysis of the results showed that in the main group of patients using the developed PGCB, there was a better dynamics in eliminating the symptoms of catarrhal inflammation after 5 and 10 days. When using the proposed treatment, the manifestations of the disease decreased by 78% by the third day and completely disappeared by the 5th-6th day. The time for the elimination of visible signs of inflammation in the main group was 5.9±0.54 days, while in the comparison group, it was 9.6±1.39 days ($p<0.05$). After 5–10 days of treatment, all examined patients showed minor statistically insignificant differences in the hygiene and PMA indices. However, the dynamics of oral hygiene indices in patients from the main group, who underwent treatment with the proposed PGCB, showed better statistically significant values after a month: OHI-S – 0.5±0.16 points, which significantly differed from the hygiene values in the comparison group (2.6±0.15 points) ($p<0.05$). The PMA and bleeding indices according to Mühlemann H.R. after 1 month in the main group were 4.08±0.4% and 0.1±0.1 points, respectively. These values differed from the comparison group, where the PMA index after a month was 22.36±1.18%; according to Mühlemann H.R. – 1.85±0.16 ($p<0.05$), indicating insufficiently positive results.

After 6 and 12 months, the index assessment in the main group of patients corresponded to the clinical norm of periodontal tissue with no periodontal pockets. A long-term clinical and radiological stabilization was achieved. In contrast, in the comparison group, the indices were statistically not different from those obtained 1 month after treatment, indicating the risk of relapse.

During the entire treatment period, no allergic reactions or other adverse effects were observed with the use

of PGCB. On the other hand, the advantage of the caps, used only in the main group, is their tight fit to the gum tissue and the retention of the gel composition as a periodontal dressing at the site of damage for a specified period.

Thus, to achieve effective clinical application, the optimal ratio of benzydamine in tablet form for resorption, a non-steroidal anti-inflammatory drug (NSAID) for local use in the oral cavity, was included in the composition of PGCB. In terms of their mechanism of action, NSAIDs are somewhat inferior to steroids, but they have low toxicity and other advantages. NSAIDs primarily act on the exudation and proliferation phases. They are inhibitors of the enzyme cyclooxygenase (COX), which affects arachidonic acid, leading to the formation of important mediators of inflammation and pain (prostaglandins and thromboxanes). Their concentration increases proportionally to the severity of the disease. The lipoxygenase metabolic pathway of arachidonic acid leads to the formation of lipoxygenase – 5-LOX. NSAIDs selectively inhibit both forms of the enzyme – COX-1 (cyclooxygenase) and COX-2. As a result, this significantly reduces hyperemia, swelling, and pain reactions and contributes to the normalization of microcirculation processes. At the same time, NSAIDs prevent the formation of microthrombi by inhibiting the synthesis of thromboxanes, slowing down the activity of hyaluronidase, and blocking serotonin receptors in the vessels. Among the mechanisms of action of NSAIDs is the ability to uncouple oxidative phosphorylation, slow down the formation of macroergic bonds due to the effect on adenosine triphosphate at the site of inflammation. The inhibition of proliferation by NSAIDs is associated with a decrease in fibroblast activity and a reduction in collagen synthesis. NSAIDs have little effect on alteration processes, but they still weaken the formation of toxic radicals that participate in the development of the inflammatory process in periodontal tissues (Newman, et al., 2019). Thus, analyzing the above, it can be concluded that the tablet form of benzydamine is a medicinal product with active anti-inflammatory, analgesic, and anti-exudative properties. When applied locally in the oral cavity, benzydamine accumulates in inflamed tissues, where effective concentrations are achieved due to the ability of the drug to penetrate through the mucosa.

In the developed PGCB composition, another active component, comb drug drops, a direct-acting antiviral and antimicrobial drug for internal and local application (as an application to mucous membranes), was included. 1 ml of the drops contains 1 ml of liquid extract from the grass of *Deschampsia caespitosa* and *Calamagrostis epigeios* (1:1). The flavonoids in this drug have the ability to inhibit the replication of DNA and RNA viruses *in vitro* and *in vivo*. The antiviral action of the drug against herpes, hepatitis, papillomaviruses, HIV, flu, and various acute respiratory infections has been proven. Its direct antiviral action mechanism is the inhibition of virus-specific enzymes (DNA and RNA polymerases, thymidine kinase, reverse transcriptase, and neuraminidase). This drug has pronounced immunotropic properties due to its plant flavonoid complex, protects mucous membranes, and normalizes local immunity indicators (secretory immunoglobulin A, lysozyme, lactoferrin, and C3 complement component), as reflected in the literature (Carvalho, et al., 2021). Moreover, this drug induces the synthesis of endogenous α- and γ-interferons to a physiologically active level, which significantly enhances the nonspecific resistance of the body to viral and bacterial infections (Matyash, et al., 2019; Beketova, et al., 2021), while not exhibiting immunotoxic effects or causing refractoriness (hyporesponsiveness) of the immune system. The drug has antioxidant activity and can inhibit the course of free radical processes, preventing the accumulation of products of lipid peroxidation. The antioxidant status of the cell increases, intoxication decreases, and the recovery processes in the body after infection improve.

Sodium alginate, included in PGCB as the gel base, is the sodium salt of natural alginic acid, isolated from brown seaweed. The drug is environmentally harmless, hypoallergenic, does not absorb into the bloodstream, and is well-tolerated by the body. In medicine, alginic acid salts have the following therapeutic properties: immunostimulant – protects against infections and tumors; hemostatic – wound healing for bleeding wounds; adsorbent – removal of radionuclides and heavy metals from the body; regenerative – restoring skin and mucous membranes in cases of burns, bedsores, etc.; antihistamine – preventing allergies; binding – removing cholesterol from the body.

Since alginate hydrogels are relatively easily degraded by microbial contamination, preservatives should be used. nipagin (methylparaben, 0.1%) was introduced into the developed PGCB as a preservative with antimicrobial activity.

Thus, the developed gel composition, combining such active components as a flavonoid plant complex and benzydamine hydrochloride, contributed to the improvement of periodontal status in orthodontic patients in the main group, as confirmed by clinical observations with the applied diagnostic indices, and is consistent with the data presented in the global literature (Liu, et al., 2024; Tanaka, et al., 2008; Sparrow, et al., 2020).

Conclusions. The obtained clinical results characterize the proposed extemporaneous gel composition

based on plant flavonoids and benzydamine hydrochloride as a pathogenetically justified and highly effective agent that optimizes and accelerates the healing process, with intensive anti-inflammatory properties. Due to its improved composition and quantitative ratio of components, the composition ensures the absence of side effects, reduces treatment time due to the prolonged action of alginate and individually made caps, and has broad practical applications for dentistry and periodontology. The developed agent allows for the elimination of the inflammatory process and long-term stabilization of periodontal tissue diseases up to 12 months.

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Hodovanyi O.V. – idea, research design, literature collection and analysis, participation in preclinical studies, organization, and implementation of clinical studies;

Martovlos A.I. – statistical calculations; abstracts, conclusions, summaries; participation in article writing;

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