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CURRENT REGENERATIVE APPROACHES TO THE TREATMENT OF GENERALIZED PERIODONTITIS IN YOUNG PEOPLE (LITERATURE REVIEW)

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Abstract. *Current regenerative approaches to the treatment of generalized periodontitis in young people (literature review). Korchak O.V., Kovach I.V., Litvinova Y.V., Yanishevsky K.A., Marchenko N.S. Periodontal diseases are a component of the global burden of chronic morbidity worldwide. The prevalence of periodontitis increases with age, reaching a high at the age of 40, which has increased medical and social importance. In Ukraine the prevalence of periodontal diseases among people aged 19-24 reaches 30%, 25-30 years – more than 60%, and in the age group 35-44 years and older – varies from 92 to 98%. With the generalized form of periodontitis in young people, considerable degradation of periodontal tissues occurs, while treatment measures are mainly ineffective, with a temporary therapeutic effect that only stabilizes the course of disease. The goal of this literature review was to identify innovative approaches to the reparation and regeneration of affected periodontal tissues that could be used as non-invasive treatment modes. The conducted analysis included studies whose findings were published in 52 English- and Ukrainian-language information sources for the period 1985-2022. The literature search was carried out in the PubMed, Scopus, Google Scholar databases and in the electronic catalog of the National Scientific Medical Library of Ukraine. The results of the literature review confirm the considerable potential of cell therapy supplemented with platelet-rich plasma for the formation of new periodontal tissues, which supported their use to promote the regenerative process. In combination with stem cells, platelet-rich plasma provides a considerable increase in the effectiveness of periodontal disease treatment in young people. The literature search was carried out in PubMed databases (327 sources), Scopus (121 sources), Google Academy (16 articles) and in the electronic catalog of the National Scientific Medical Library of Ukraine (89 records). Out of 537, 52 sources were selected for review. Periodontal tissue disease is an actual problem today. According to the data of the analyzed literature, the use of stem cells in dentistry is actively studied, but there are no recommendations and protocols for their use in periodontology. The analyzed scientific sources, the results of which were published in English- and Ukrainian-language sources, aimed at tissue regeneration, have a significant impact on the creation of new approaches to the treatment of generalized periodontitis. The world experience of using cellular technologies with using stem cells demonstrates the significant potential and positive results of their application to promote the regenerative process in the comprehensive treatment of periodontal diseases. The combination of stem cells and platelet-enriched plasma significantly increases the effectiveness of treatment of periodontal tissue diseases, in particular generalized periodontitis in young people. The use of stem cells and growth factors, which contains platelet-rich plasma, allows you to significantly increase the effectiveness of periodontal disease treatment.*

Реферат. *Сучасні регенеративні підходи до лікування генералізованого пародонтиту в осіб молодого віку. Коччак О.В., Ковач І.В., Літвінова Я.В., Янішевський К.А., Марченко Н.С. Захворювання пародонта є складовою глобального тягаря хронічних хвороб у всьому світі. Поширеність пародонтиту зростає з віком, досягаючи піку у віці 40 років, що має підвищену медико-соціальну значущість. В Україні поширеність захворювань пародонта серед осіб 19-24 років досягає 30%, 25-30 років – більше 60%, а у віці 35-44 роки і старше – варіює від 92 до 98%. При генералізованій формі пародонтиту в осіб молодого віку відбувається значне руйнування тканин пародонта, у той час, як лікувальні заходи переважно мають низьку ефективність, з*

тимчасовим лікувальним ефектом, що лише стабілізує перебіг захворювання. Огляд літератури проведений з метою виявлення інноваційних підходів до репарації й регенерації ушкоджених тканин пародонта, які можуть бути застосовані як неінвазивні методи лікування. Проведено аналіз досліджень, результати яких були опубліковані в англо- й україномовних джерелах інформації протягом 1985-2022 років. Пошук літератури здійснювався в базах даних PubMed (327 джерел), Scopus (121 джерело), Google Академія (16 статей) та в електронному каталозі Національної наукової медичної бібліотеки України (89 записів). З 537 для огляду було відібрано 52 джерела. Захворювання тканин пародонта – це актуальна проблема сьогодення. Згідно з даними проаналізованої літератури, використання та застосування стовбурових клітин у стоматології активно вивчається, проте рекомендації та протоколи використання їх у пародонтології відсутні. Проаналізовані наукові джерела, що досліджують регенерацію тканин, результати яких були опубліковані в англо- й україномовних джерелах, суттєво впливають на створення нових підходів до лікування генералізованого пародонтиту. Світовий досвід застосування клітинних технологій з використанням стовбурових клітин демонструє значний потенціал та позитивні результати їх застосування для сприяння регенеративному процесу в комплексному лікуванні хвороб пародонта. Комбінація стовбурових клітин та збагаченої тромбоцитами плазми істотно підвищує ефективність лікування захворювань тканин пародонта, зокрема генералізованого пародонтиту в осіб молодого віку. Застосування стовбурових клітин і факторів росту, які містить збагачена тромбоцитами плазма, дозволяє істотно підвищити ефективність лікування захворювань пародонта.

Periodontal diseases are a component of the global burden of chronic morbidity, affecting up to 80% of children and 95% of adults worldwide. The prevalence of periodontitis increases with age, with a sharp growth between the third and fourth decades of life, reaching a peak at the age of 40 years, acquiring increased medical and social importance [1]. According to various authors, in Ukraine the prevalence of periodontal diseases at the age of 19-24 years reaches 30%, 25-30 years – more than 60%, and at the age of 35-44 years and older – varies from 92 to 98% [2, 3, 4].

In a progressive form of the disease at a young age, extensive destruction of periodontal tissues occurs, which must be taken into account when developing programs for their comprehensive treatment and prevention [5]. At the same time, in most cases remedial measures have low efficiency, since the therapeutic effect is temporary and the prophylactic action is absent [6]. Moreover, traditional treatment methods are mainly oriented on stabilizing the disease, and not on regenerating destructed periodontal tissues [7].

Aim: development of innovative approaches to the reparation and regeneration of affected periodontal tissue in young people, that could be used as non-invasive methods for the treatment of generalized periodontitis.

Disease of periodontal tissues is an urgent problem of the present. According to the analyzed literature, the use and application of stem cells in dentistry is actively studied, recommendations and protocols for use in periodontology are absent. Scientific sources whose results were published in English- and Ukrainian-language sources aimed at tissue regeneration, significantly influence the creation of new approaches to the treatment of generalized periodontitis were analyzed. World experience of the application of cell technologies using stem cells demonstrates the significant potential and

positive results of their application to promote the regenerative process in the complex treatment of periodontal diseases.

The combination of stem cells and thrombocyte-enriched plasma significantly increases the effectiveness of the treatment of diseases of periodontal tissue, namely generalized periodontitis in young people. The use of stem cells and growth factors, containing plasma enriched with platelets, allows to significantly increase the effectiveness of treatment of periodontal diseases.

MATERIALS AND METHODS OF RESEARCH

The article analyzes and summarizes the data from scientific sources on optimizing the treatment of generalized periodontitis in young people using regenerative medicine. The analysis of studies, the results of which were published in English and Ukrainian-language sources of information during 1985-2022, was carried out. Using keywords in the open access resources PubMed, 327 sources were reviewed, of which 26 were relevant to the purpose of the study; Scopus – 121 sources, of which 10 were used for the review; 16 sources were selected in the electronic catalog of the National Scientific Medical Library of Ukraine (89 records), the full text of which was found in Google Academy. Thus, 52 sources out of 537 were selected for the review. At the same time, only a few articles are devoted to the combined use of platelet-rich plasma and mesenchymal stem cells, which justifies the need for further in-depth research.

The literature review was carried out in accordance with the principles of bioethics set forth in the Helsinki Declaration for the Ethical Principles of Medical Research Involving Human Subjects and the Universal Declaration on Bioethics and Human Rights (UNESCO). An extract from the minutes of the meeting of the bioethics committee on June 15, 2020 was received.

RESULTS AND DISCUSSION

To date, complete regeneration of periodontal defects remains complex and unpredictable, as it requires maximal recovery of epithelium, gingival connective tissue, periodontal ligament (PDL) and alveolar bone. Various regenerative strategies have been proposed, including the use of biological agents that regulate inflammation and improve healing, and increase the volume of regenerated bone as well [8]. Some bioactive molecules and materials have been clinically used to regenerate destructed periodontal tissues as non-invasive methods for treating generalized periodontitis by introducing cells of different origins and cell products based on them into the body [9]. However, the indications and extent of tissue regeneration with these treatment methods are limited, and the need for a new regenerative approach to the therapy of affected periodontal structures in young people remains.

In recent years, the use of stem cells (SC) for periodontal regeneration has been actively studied, but clinical practice is not yet standardized and there are no recommendations for the use of SC in periodontology. Compared with traditional regenerative therapy, SC in tissue engineering demonstrates considerable advantages in regenerating of periodontal defects and may allow for complete recovery of the periodontium [10, 11]. F. Citterio et al. (2020) described the basic SC populations used for periodontal regeneration, including ones derived from bone marrow, adipose tissue, and the basic SC populations derived from dental tissues: SC PDL, dental pulp SC, SC from lost deciduous teeth, SC of apical papilla and precursor cells of tooth follicles. The studies of SC application for tissue regeneration have considerably influenced therapeutic strategies for inflammatory and destructive diseases of parodontium [12].

The identification of SC PDL (2004) led to a new step in periodontal regeneration, as it was suggested that SC PDL could potentially form cementum/PDL-like tissue *in vivo*. Transplantation of SC PDL, which is obtained from an easily accessible tissue resource, has become considered a promising therapeutic measure for the regeneration of periodontal tissues [13]. In 1985, A.H. Melcher proposed the concept that SC exist in periodontal tissues [14]. Since then, it has been found that other SC can promote the regeneration of periodontal tissues under appropriate induction conditions [15]. Thus, PDL-derived cells have the characteristics of mesenchymal SC (MSC), which have been named PDL-MSC. The ability of PDL-MSCs to differentiate into both osteoblasts and adipocytes with a small chondrogenic potential, has been shown [16]. Cultivation in an osteoinduced

environment enhances the ability of PDL-MSC for periodontal regeneration [17].

It has been established that MSC for periodontal tissue regeneration can be derived from bone marrow (BMSC), adipose tissue, skin, and oral tissue [18]. R. Monterubbianesi et al. (2019) investigated *in vitro* the differentiation potential of dental pulp SC (DPSC), gingival fibroblasts, and foreskin fibroblasts. These cells were cultured in media of osteogenic and adipogenic differentiation. While in whole fibroblasts are more prone to adipogenic differentiation, DPSCs have a higher osteogenic potential and are most suitable for regenerative purposes involving bone and dental tissues [19]. S.A. Tassi et al. (2017) in a systematic review of articles (22 studies), evaluated the periodontal regenerative potential of MSC in animal models [20]. Autologous, allogeneic and xenogeneic MSC were used to promote periodontal regeneration. Among them: BMSC, SC PDL, MSC, DPSC, pluripotent SC, MSC from dental cementum, alveolar periosteal cells. SC PDL convincingly promoted the regeneration of PDL and cementum. Also, the additional use of MSC improved the outcomes of periodontal defect repair when using membranes or bone substitutes. The authors considered it to be proven that the use of MSC has a beneficial effect on periodontal regeneration, and the differences in success rates may be due to the use of heterogeneous cells, i.e. future studies should aim to establish phenotypic profiles of highly regenerative MSC populations [20].

L.L. Zhou et al. (2020) considered oral BMSC to be promising for further application in regenerative dentistry, emphasizing that in addition to the excellent regenerative potential they can interact with the surrounding inflammatory microenvironment, exerting an immunomodulatory effect in the treatment of periodontitis [21].

F. Ferrarotti et al. (2018) evaluated whether DPSC delivered into intraosseous defects would improve clinical and radiographic parameters of periodontal regeneration (n=29). Patients were divided into following groups: in the test group (n=15) the defects were filled with DPSC applied on the collagen sponge, while in the control group (n=14) only the collagen sponges were used. The test group showed a more pronounced decrease in probing depth (PD) (4.9 mm vs. 3.4 mm), an increase in the clinical attachment level (CAL) – 4.5 mm vs. 2.9 mm, and filling the bone defects (3.9 mm vs. 1.6 mm) than in the control. Moreover, residual PD < 5 mm (93% vs 50%) and CAL elevation ≥ 4 mm (73% vs 29%) were also more frequent in the test group. The authors claim that the DPSC application considerably improved clinical parameters of periodontal regeneration 1 year after treatment [22].

An alternative source of SC is adipose tissue. SC derived from adipose tissue (ASC) were classified as MSC based on their morphological and cultural characteristics [23]. In 2001, ASC was discovered at first by P.A. Zuk et al. From 300 ml of adipose tissue, the authors obtained from 10 to 20/106 ASC. Fragments of adipose tissue were incubated at 37°C in a 0.075% collagenase type I solution for 30 minutes. After centrifugation, the primary suspension was divided into two fractions. Adipocytes were placed in the upper light layer, and in sediment-precipitated cells of the stromal-vascular fraction: preadipocytes, endothelial and smooth muscle cells of blood vessels, perivascular fibroblasts and a supporting fibrous collagen stroma with an admixture of hematopoietic cells. Erythrocytes were removed by incubation in a lytic chloride solution, and other hematopoietic cells with weak adhesive ability were eliminated by passivation [24].

The simplicity and low-traumatic nature of lipospiate obtaining, the large number of derived cells, the absence of an adverse effect of the donor's age on the proliferative and differentiation potential of cells, and the preservation of the cell properties after freezing provide the advantages of ASC [25]. Today, ASC are recognized as the most popular source of adult SC populations for osteogenesis due to the simplicity, safety, and availability of isolation, which are almost indistinguishable from BMSC in terms of proliferative and differentiation properties. Also, the advantage of ASC for clinical applications is that the physical and mental burden on the patients during sample collection is very small compared to BMSC, and the source of ASC can be sampled safely and in sufficient quantity [26, 27]. Despite some disparity of opinions, most authors support the hypothesis that ASC is a promising object for autologous transplantations [28, 29, 30].

Thus, at the current stage of periodontitis treatment, attempts are made to simultaneous restoration of all periodontal structures, and methods of tissue engineering and directing tissue regeneration are being actively implemented. Cell cultures are used, which increase the activity of regenerative processes. The world experience of using cell technologies with SC demonstrates the positive results in the therapy of periodontal diseases. However, further study of their mechanism of action, searching for the optimal carrier and methods of introduction into the body, clarification of clinical indications and contraindications for use is required.

Regeneration or recovery is an expected effect of healing after periodontal therapy. The concept of using regenerative therapies of inflammatory and destructive lesions in the periodontium is based on restraining pathological progression with concomitant restoration

of affected tissues [31]. The use of MSC in clinical settings is limited by the need for growth factors for their growth and spreading, the low exit of MSC at isolation (usually 0.001-0.01%) and the heterogeneity of their multidifferentiation potential, i.e., a catalyst that can accelerate their differentiation and proliferative potential is extremely important [32].

One of these methods is injection stimulation of regenerative processes using autologous platelet-rich plasma. Since the late 1980s, R.E. Marx has used autologous platelet-rich plasma in periodontal tissue diseases because it promotes bone and soft tissue healing. According to the author, platelet-rich plasma (PRP) was defined as a content of 1×10^6 platelets/ μ l in a 5 ml volume of plasma [33]. PRP is considered as a "first generation" of platelet concentrate. Platelet concentrates are biologic autologous products derived from the patient's whole blood and mainly contain a supraphysiological concentration of platelets and growth factors. These platelet concentrates have anti-inflammatory and healing properties [34].

The wound healing cascade is initiated by thrombus formation, followed by a proliferation stage and a maturation stage. Growth factors promote wound healing by increasing cell proliferation (mitogenesis), cell migration (chemotaxis) and stimulating the formation of new blood vessels (angiogenesis) [33]. There are more than 15 growth factors with their isoforms present in PRP. At the same time, stimulation of periodontal tissue regeneration processes occurs due to such growth factors as platelet-derived growth factors (PDGF- α , PDGF- β , PDGF- $\alpha\beta$), transforming growth factors (TGF- β 1, TGF- β 2), vascular endothelial growth factor (VEGF), epithelial growth factor (EGF), etc., which are contained in platelets [33]. When platelets are activated, various growth factors that promote wound healing are released. The advantage of PRP is the release of a considerably larger number of growth factors at earlier time points (after 15-60 minutes of incubation) [35]. In addition, I.V. Kovach and N.V. Gutarova examined 48 patients aged 18 to 25 years with chronic catarrhal gingivitis. At the baseline, an increase in linear and volumetric blood flow rates in patients were detected (compared to the age reference). The follow-up results showed that PRP alone had a significant effect on the studied blood flow parameters immediately after treatment, while traditional methods of therapy had no effect on blood supply. It was concluded that PRP provides normalization of the linear and volumetric blood flow rates due to the ability to stimulate microcirculation and improve the rheological properties of blood [36].

It has also been suggested that various growth factors produced by PRP considerably enhance the

paracrine effect of ASC and this may be a more effective approach than cell therapy alone. *In vitro* study showed that the addition of PRP considerably increased the level of growth factors secreted by ASC. Transplantation of the ASC/PRP mixture considerably changed the bone regeneration for a long time. In addition, some ASC straightly differentiated into osteogenic cells *in vivo*. These findings suggest that the ASC/PRP combination has an additional effect on bone regeneration [37].

Variability in PRP depends on the concentration of other cell types such as WBC and RBC. If a native hematoma consists of 95% of erythrocytes, then a clot formed by leukocyte-depleted PRP contains 95% of platelets, 4% of erythrocytes and 1% of leukocytes. Centrifugation to obtain PRP dramatically reduces or completely removes erythrocytes [38]. The need for leukocyte preservation in PRP is widely discussed, and the results of trials of leukocyte-rich PRP versus pure (leukocyte-depleted) PRP are controversial. According to the review of B.W. Oudelaar et al. (2019), most commercial kits contain leukocyte-rich PRP. Also, the authors emphasize that the presence of leukocytes has both beneficial and adverse effects, and that the content of leukocytes must be matched with the specific clinical application [39]. Regarding bone regeneration, it has been shown that leukocyte-rich PRP can stimulate osteogenic differentiation and proliferation of MSC *in vitro* in a dose-dependent manner compared to leukocyte-free PRP [40]. According to A.P. Samadi et al. (2019), high leukocyte concentrations in PRP slow bone healing by inducing an inflammatory response that can become chronic, while low concentrations of WBC do not stimulate a sufficient inflammatory response necessary for early bone regeneration [41]. According to these conflicting reports, the effect of leukocyte content in PRP on bone healing is still unknown.

The production of PRP is not standardized, so it has been reported about numerous PRP protocols with considerable variations in anticoagulants, centrifugation techniques, and activation methods. Centrifugation protocols can include one ("soft" spin) or two ("soft" and "hard" spins) centrifugations with variable speed and time. Platelets can be endogenously activated by freeze-thaw cycles to damage the platelet membrane, but exogenous activation of platelets by thrombin or calcium chloride is more common [42].

PRP is obtained by centrifugation of autologous peripheral blood. A cell separator samples 400-450 ml of blood through a central venous catheter.

Introduction of anticoagulants and heterologous promoters prior to centrifugation initiates polymerization, which occurs rapidly but also results in the rapid release of large amounts of growth factors, and tends to be highly depleted within days [43]. Due to the osteogenic growth factors in PRP, it has been hypothesized that PRP may act synergistically with MSC to promote osteogenesis [44].

Centrifugation is carried out at 1300 rpm for 10 minutes ("soft" spin). The second centrifugation – at 2000 rpm for 10 minutes ("hard" spin). After 10 minutes of centrifugation, three layers are obtained. The least dense layer, which is platelet-poor plasma, makes up about 45% of the sample; the middle layer consists of erythrocytes and makes up about 40% of the sample; and the bottom layer – PRP – about 15% of the sample [45].

Most often, PRP is defined as plasma with a concentration of platelets approximately 2-5 times higher than in whole blood (up to 1 million platelets in 1 μ l of blood plasma), due to which the concentration of growth factors secreted by platelets increases; this stimulates angiogenesis, attracts undifferentiated SC to the affected area and induces the division of cells involved in tissue regeneration. Therewith PRP production protocols can be corrected to obtain PRP with higher or lower platelet concentrations. It has been scientifically substantiated that the stimulating effect of PRP is manifested at a platelet concentration of 1,000,000/ μ l. At lower concentrations, the stimulating effect is not achieved. At the same time, it has not yet been demonstrated whether increasing the concentration of platelets above 1,000,000/ μ l facilitates regeneration [32].

Y. Yamada et al. (2006) applied MSC/PRP gel on the root surface of the tooth and adjacent defects. Re-examination showed that treatment by application of MSC/PRP gel on periodontal areas with angular defects resulted in a 4 mm decrease in probing depth and a 4 mm increase in CAL with disappearance of bleeding and tooth mobility. Radiographic assessment showed a decrease in the depth of bone defects. The interdental papillae have recovered. The authors claim that the use of MSC in PRP gel is useful for the regeneration of periodontal tissues, for the treatment of esthetically sensitive areas, and for reducing patient morbidity [46]. In another study (2013), the authors studied the combination of BMSC with PRP for periodontal tissue regeneration. The combination of BMSC with PRP was transplanted in 17 patients. A decrease in probing depth, an increase in CAL, and an extension in newly formed bone tissue were observed, although the shape of the defect was not mentioned [47].

M. Tobita et al. (2013) studied the transplantation of ASC into periodontal defects using PRP as a scaffold material in animal models and confirmed the regeneration of periodontal tissues by means of mixed transplantation of ASC and PRP. PRP contains various growth factors and may be useful as a cell carrier in the ASC treatment [48]. In another study, the authors are trying to evaluate the suitability of this cell therapy for periodontal tissue regeneration. The primary outcome is to examine alveolar bone height after mixed ASC/PRP transplantation into a vertical alveolar bone defect caused by moderate or severe periodontitis in patients (n=10) after initial periodontal therapy. The study is comparative between the ASC/PRP transplantation group and the standard therapy group (n=5). In patients in the ASC/PRP transplantation group, approximately 50 mL of subcutaneous adipose tissue is aspirated from the abdomen or buttocks under local anesthesia. The study is still ongoing, but the authors believe that if this cell therapy using autologous MSC is effective, it may become a promising technology for the regeneration of periodontal defects [49].

J. Yamakawa et al. (2017) evaluated the optimal method of PRP and BMSC using. BMSC were cultured with different concentrations of PRP to assess cell proliferation and osteogenic differentiation. BMSC proliferation increased in a PRP-concentration-dependent manner. The rate of new osteogenesis due to BMSC and PRP (platelets $100 \times 10^4 / \mu\text{L}$) was 46.9% during 8 weeks, which was considerably greater compared to the high ($500 \times 10^4 / \mu\text{L}$) or low ($20 \times 10^4 / \mu\text{L}$) concentrations, as well as when BMSC or PRP are used separately. Author concluded that increasing the PRP concentration does not stimulate proliferation and migration of cells [50]. The study of A.T.M. Nguyen et al. (2019) showed that at 5% PRP, BMSC multiplied with considerably bigger number of cells than at other concentrations (1 %, 2%) on day 5, 7 and 9 of culturing. The authors argue that due to the demonstrated considerable enhancement of proliferation and migration of cells, a level of 5% RPR may be optimal and this concentration can be used to enhance the BMSC potential in bone regeneration, wound healing, and bone defect repair [51]. The relatively new biotechnology of the combined application of SC and PRP is one of the tissue engineering methods that is attracting more and more attention from the medical community [52].

Thus, the efficacy of PRP for periodontal regeneration is still debated in the literature. In some

cases, various periodontal procedures on both soft and hard tissues were included, while other authors specifically focused on intraosseous defects. Some authors have reported a beneficial effect of PRP in terms of increasing CAL and reducing PD.

CONCLUSIONS

1. Periodontal diseases are a component of the global burden of chronic morbidity, affecting children and adults worldwide. Ukraine is no exception. At the same time, the prevalence of periodontitis increases with age, with a sharp surge between the third and fourth decades of life, acquiring increased medical and social importance.

2. Regeneration of periodontal defects remains a complex and unsolved problem, as it requires maximum restoration of the epithelium, gingival connective tissue, periodontal ligament and alveolar bone. Various regenerative strategies have been proposed for the treatment of generalized periodontitis, also at a young age. One of these methods is injection stimulation of regenerative processes using stem cells and autologous platelet-rich plasma.

3. The results of literature review confirm the considerable potential of cell therapy in combination with platelet-rich plasma for the formation of new periodontal tissues, which substantiates the use of this approach to promote the regenerative process. The combined use of stem cells and growth factors in platelet-rich plasma considerably improves the effectiveness of periodontal disease treatment.

4. However, using platelet-rich plasma restricts a complex protocol of preparation, lack of standardization in the preparation protocol, variations in the storage time of different concentrations of platelets, and life-threatening coagulopathies. Also, the effectiveness of treatment for each form of the disease is not well-defined, which requires further in-depth studies.

Contributors:

Kopchak O.V. – supervision;
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Litvinova Y.V. – writing;
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