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Impact of an oxygen-releasing agents and supportive hygienic aids on the periodontal pocket microbiota during the treatment of patients with stage III-IV periodontitis: clinico-microbiological study

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Abstract

Background. Taking into account that oxygen-releasing agents are relatively new in the periodontal practice it seems to be clinically relevant to validate how such may impact the results of classical periodontal treatment approaches, if latter are modified by the additional use of active oxygen-containing substances as local therapy modality. Moreover, effect of oxygen-releasing substances used in periodontology needs to be quantified not only through the changes of clinical criteria, but also through the changes of microbiological parameters registered with the precise laboratorial approach.

Objective. To provide comparative quantitative assessment of periodontal pocket microbiota changes among patients with III-IV stages of periodontitis after modification of standard scaling and root planning approaches by application of oxygen-releasing gel with supportive hygienic aids and compare effect of such with chlorhexidine-containing agents.

Material and Methods. Patients with III-IV stages of periodontitis were randomly allocated either to control (20 subjects) or study group (20 subjects). Independently of group allocation all patients underwent basic non-surgical periodontal treatment according to the EFP protocols (subgingival instrumentation). Patients within control group additionally to the basic non-surgical periodontal treatment received post-instrumentational application of chlorhexidine gel into the periodontal pockets immediately after cleaning. Patients within study group additionally to the basic non-surgical periodontal treatment received post-instrumentational application of an oxygen-releasing gel, which was applied immediately after subgingival instrumentation into the periodontal pockets. The microbiological assessment of the periodontal pocket biotope was performed using the PeriodontScreen Real-time PCR test. Samples for the study were collected at different time points: before treatment, two weeks after treatment, and two months after treatment.

Results. Two months after treatment Aggregatibacter actinomycetemcomitans reappeared, although in smaller quantities, in 90% of patients in the control group, however, in the study group, among patients in whom Aggregatibacter actinomycetemcomitans was not detected after two weeks, it remained undetectable even after two months. Overall, Aggregatibacter actinomycetemcomitans was identified in only 20% of the patients in the second group after two months. No significant difference in the average quantitative levels of Porphyromonas gingivalis and Porphyromonas endodontalis between two groups were observed at different time points ($p > 0.05$).

Conclusions. Considering limitations of present study, provided analysis of the obtained data revealed that oxygen-based preparations exhibit antibacterial properties no less effective than chlorhexidine-based preparations, which allows to recommend such as additional treatment modalities for local application and home hygiene aid during complex treatment of patients with periodontitis. Taking into account registered detection levels changes after provided treatment it may also be assumed that oxygen-releasing gel demonstrated the most pronounced antibacterial properties against such pathogens as Aggregatibacter actinomycetemcomitans and Treponema denticola, particularly in 2 months long monitoring.

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Introduction

Chlorhexidine (CHX) is an antimicrobial agent that is often prescribed for local application during dental treatment in forms of gels, toothpastes, and mouthwashes. Chlorhexidine-based products have been studied for over four decades, and CHX itself has been considered as "gold standard" for controlling bacterial biofilm within the oral cavity [1, 2]. However, there is ongoing debate among scientists as to whether chlorhexidine still deserves the title of "gold standard" nowadays [3]. Despite convincing evidences regarding usage of chlorhexidine in the form of mouthwash for 4–6 weeks, and sometimes up to 6 months, which enhances the effect of mechanical in-home tooth brushing and reduces plaque accumulation, several studies have shown that CHX demonstrates side effects such as tooth staining, taste disturbances, and calculus formation after prolonged use for more than 4 weeks [1, 2, 3, 4]. Additionally, it has been reported that the usage of chlorhexidine for wound treatment is limited due to its cytotoxicity toward human fibroblasts [4]. Several studies have reasoned the potential of using products based on triclosan, cetylpiridinium, aloe vera extract, tea tree oil, and other plant essential oils with therapeutic antibacterial effects, for additional plaque control both for professional and home oral hygiene [5, 6, 7, 8, 9, 10, 11, 13]. General tendency demonstrates continuous intention for searching and developing products that provide additional effects on biofilm, thereby improving the quality of treatment for patients with inflammatory periodontal tissue diseases.

Relatively recently several studies reported the results of using products with active oxygen as the main active component for local antibacterial action during periodontal treatment. Preliminary research on toothpastes containing active oxygen and lactoferrin has shown a reduction in the colony-forming units of bacteria, yielding results comparable to those of chlorhexidine [12]. Different forms of active oxygen demonstrate strong chemotactic effect on leukocytes, responsible for lipid peroxidation of bacterial cell walls, and cause disruption of respiratory burst of neutrophils in wounds or fluids. Therefore, it is considered a broad-spectrum and nonspecific antibacterial agent [14].

Among several new products based on active oxygen-releasing mechanism, Blue®M product line (gel, toothpastes, mouthwashes of varying concentrations, and an oral foam), developed by Bluem International (Weinfeld, Netherlands), have been demonstrated increasing body of evidences that proves its effectiveness in clinical conditions [15-20]. Previously it has been reported that oxygen-releasing agents, such as Blue®M intraoral gel, support significant reduction of periodontal pockets' depth, and responsible for decrease within inflammation pattern due to the release of active oxygen itself [16, 18, 19]. But there is a lack of targeted studies which aimed at objectifying the impact of oxygen-releasing products on the bacterial microflora within periodontal pockets, and how microbial proportions are changing under the influence of active oxygen substance.

It is important to highlight that none of the mouthwashes, toothpastes, or gels work in isolation from the essential periodontal treatment, which is based on subgingival instrumentation [21, 22]. These procedures are aimed at removing biofilm and dense dental deposits from all tooth and root surfaces, creating a biocompatible root surface suitable for the restoration of clinical attachment levels, and further recolonization with the balanced microflora [21, 22, 23].

After the introduction of a new classification of periodontal and peri-implant tissue diseases into clinical practice by the World Workshop in 2017, the European Federation of Periodontology (EFP) published S3 Clinical Practice Guidelines for the Treatment of Stage I-III Periodontitis in 2020, edited by Prof. Mariano Sanz and David Herrera et al. [24]. In 2022, the S3 Clinical Practice Guidelines for the Treatment of Stage IV Periodontitis were published, edited by Prof. David Herrera and Mariano Sanz et al. [25]. The S3 level represents the highest standard of evidence and scientific validation for these treatment approaches. Comprehensive treatment protocols described in above-mentioned guidelines involve combination of systemic and local therapies aimed at improving and correcting condition of periodontal tissues.

Taking into account that oxygen-releasing agents are relatively new in the periodontal practice it seems to be clinically relevant to validate how such may impact the results of classical periodontal treatment approaches, if latter are modified by the additional use of active oxygen-containing substances as local therapy modality. Moreover, effect of oxygen-releasing substances used in periodontology needs to be quantified not only through the changes of clinical criteria, but also through the changes of microbiological parameters registered with the precise laboratorial approach.

Null hypothesis of the present study was formulated as follows: use of oxygen-releasing gel as local intrapocket treatment modality and supportive hygienic aids additionally to the standard scaling and root planning (SRP) procedure does not provide any significantly different changes within periodontal pocket microbiota compared to the usage of the chlorhexidine-containing agents for the same purpose and with the same manner among patients with III-IV stages of periodontitis.

Objective

To provide comparative quantitative assessment of periodontal pocket microbiota changes among patients with III-IV stages of periodontitis after modification of standard scaling and root planning approaches by application of oxygen-releasing gel with supportive hygienic aids and compare effect of such with chlorhexidine-containing agents.

Materials and Methods

Study design

Present research was realized in the form of prospective clinical study following adapted STROBE checklist, while also considering specifics of its realization as clinico-microbiological study. Study cohort was formed out of patients who visited Dental Clinic «Lumiere Perio Dental» (Kyiv, Ukraine). Following parameters were used as inclusion criteria: 1) established diagnosis of periodontitis stage III-IV as per EFP diagnostic guidelines; 2) minimal age of 18 years; 3) no systematic disease or conditions which may significantly impact patients' immune host response on the provided treatment; 4) no periodontal treatment during the period of previous 6 months; 5) no antibiotic use during the period of last 3 months; 6) no anti-inflammatory drugs intake on the constant bases during the period of last 3 months; 7) patient's agreement to undergo complex periodontal treatment as per proposed protocol; 8) voluntarily agreement to take part in the present research approved by the signature of informed consent form.

Taking into account above-mentioned inclusion criteria study cohort was formed out of 40 patients aged 30-55 years with the following gender distribution: 18 females and 12 males. Patients were randomly allocated either to control (20 subjects) or study group (20 subjects). Independently of group allocation all patients underwent basic non-surgical periodontal treatment according to the EFP protocols (subgingival instrumentation (SI) using a combination of an ultrasonic device with periodontal tips and Gracey mini curettes).

Patients within control group additionally to the basic non-surgical periodontal treatment received post-instrumentational application of chlorhexidine gel (Gingival Gel 0.2% chlorhexidine fluoride, TePe, Sweden) into the periodontal pockets (PP) immediately after cleaning. As for home oral hygiene, patients in control group were prescribed toothpaste (Paroex GUM, SUNSTAR EUROPE, Sweden) and a mouthwash (Paroex GUM, SUNSTAR EUROPE, Sweden), which contained CHX. During the first two weeks, the CHX concentration in toothpaste and mouthwash was 0.12%, and for the next two months, it was reduced to 0.06%.

Patients within study ground additionally to the basic non-surgical periodontal treatment received post-instrumentational application of an oxygen-releasing gel (Blue®M intraoral gel, BlueM, Wijhe, Netherlands), which was applied immediately after SI into the periodontal pockets. For home oral hygiene over the next two months, the patients were BlueM (BlueM, Wijhe, Netherlands) and BlueM mouthwash (BlueM, Wijhe, Netherlands) with active oxygen.

Microbiological assessment

The microbiological assessment of the periodontal pocket (PP) biotope was performed using the PeriodontScreen Real-time PCR test. Samples for the study were collected at different time points: before treatment, two weeks after treatment, and two months after treatment. In both groups, samples were taken using paper points and Eppendorf tubes from four sites in the oral cavity, adhering to the methodology for PCR material collection [26, 27, 28].

Both quantitative and qualitative assessment of the periodontal pocket biotope were perfromed, specifically identifying the following microorganisms: Aggregatibacter actinomycetemcomitans, Porphyromonas gingivalis, Porphyromonas endodontalis, Treponema denticola, Fusobacterium nucleatum, Tannerella forsythia, and Prevotella intermedia.

Quantitative assessment and interpretation of the obtained results were carried out according to the Table 1, recommended by the manufacturer of the PeriodontScreen Real-time test system.

Table 1. Quantitative Assessment of the Periodontal Pocket Microbiota

Abbreviation	Pathogen	Limit (copies/ml)	Clinical significance
Aa	Aggregatibacter actinomycetemcomitans	10*4	High risk of disease development. May lead to bone tissue destruction. Associated with aggressive forms of periodontitis and gingivitis.
Pg	Porphyromonas gingivalis	10*5	High risk of disease development. Produces proteases, endotoxins, and cytotoxins, damaging the integrity of the gums and bone tissue. A key disease marker alongside A.a.
Tf	Tannerella forsythia	10*5	High risk of disease development. Produces virulence factors (proteases, lipopolysaccharides). May suppress the immune system and contribute to the progression of the disease into a chronic form.
Td	Treponema denticola	10*5	High risk of disease development. Facilitates the adhesion of other pathogens. Often appears at the onset of rapidly progressing disease.
Pd	Porphyromonas endodontalis	10*6	Moderate risk of disease development. Produces active enzymes and metabolites. May inhibit phagocytosis and impair local immunity.
Fn	Fusobacterium nucleatum	10*6	Moderate risk of disease development. Appears during acute periodontal diseases, especially gingivitis.
Pi	Prevotella intermedia	10*6	Moderate risk of disease development. Plays a role in the formation of the biofilm framework, facilitating the adhesion of pathogenic bacteria. Exhibits pathogenic properties at high concentrations.

The material was delivered to the laboratory using disposable sterile paper points placed in sealed plastic Eppendorf tubes with a volume of 1.5 mL, one paper point per tube. If the time from collection to delivery exceeded 2 hours, the samples were stored in a refrigerator at a temperature of 6±2°C. No transport medium was used.

This method was used to eliminate additional, even minimal, dilution of the material during the study. It is now known that DNA is more stable during transport and storage compared to RNA, which eliminates the need for a transport medium. Furthermore, by dividing the material immediately into individual Eppendorf tubes, cross-contamination of the samples is prevented, and subsequent sample processing is simplified. Each tube was properly labeled and accompanied by a referral form containing the necessary information.

At the pre-processing stage, 100 µL of sterile 0.9% sodium chloride solution was added to each tube containing a paper point using sterile disposable tips with aerosol filters, as recommended for use in PCR laboratories. The tubes were left at room temperature for 20 minutes to allow the extraction of microbial mass into the solution. Every 5 minutes, the tubes were vortexed for 3–5 seconds to enhance the extraction process. After the extraction process, the tubes were centrifuged on a vortex at 1000 rpm for 30 seconds to settle the droplets. Afterward, the paper point was removed from the tube using sterile tweezers, carefully squeezed against the walls of the tube to remove excess liquid and then disposed in a container with a disinfectant solution. Then we added to the tubes with the extract 100 µL of lysis solution and then extracted nucleic acids using the precipitation method according to the manufacturer's recommended instructions.

The obtained nucleic acid samples were transferred to the amplification room, where amplification was performed according to the instructions for the reagent kit used to detect opportunistic microorganisms of the oral cavity by real-time PCR. The PCR kit included an endogenous internal control, in each reaction tube containing the PCR master mix.

The endogenous internal control detects a sequence of human genomic DNA, which should always be present in each extracted sample. This approach allows for monitoring not only potential reaction inhibition but also the accuracy of clinical sample collection, the efficiency of sample preparation, and analytical errors (such as a missing sample in the amplification mix). In all tested samples, the internal control functioned correctly.

After amplification, the quantity of each microorganism was calculated using the indicator cycle value, determined by the software. This calculation was based on a panel of positive standards with known concentrations. The microbial load was measured in copies per 1 mL.

Organoleptic evaluation

All patients from study and control groups completed originally developed questionnaire, aimed at evaluating organoleptic properties of the products (oxygen-releasing mouthwash and chlorhexidine-containing mouthwash) and registering patients' feedback.

In the questionnaire, each patient from both groups was asked to answer following three questions:

1. Did you find the mouthwash pleasant in taste?
2. Did you experience any unpleasant symptoms by the end of the second week, such as staining or taste disturbances?
3. Was the mouthwash better than those you had used before?

Statistical analysis

Statistical processing and comparative analysis of data representing different periopathogens' concentrations and detection levels was carried out using basic inferential statistics principles. Frequency of pathogen detection in all patients from both groups at different time points was assessed in percentage values, and obtained values were compared between study and control group.

Significancy of the calculated differences among detection levels and concentrations levels of periopathogens, observed at various monitoring time periods, was measured using Student's t-criterion for parametrical variables and Mann-Whitney's U-test for nonparametric variables. Observed outcomes were classified as statistically reliable only under condition of $p < 0.05$ (significance level of 0.95).

Results

Analysis of periodontal pocket biotope of all patients carried out with PeriodontScreen test before treatment has shown no statistical differences between study and control groups in regard to all targeted periopathogens both for the detection levels and concentrations rates ($p > 0.05$).

Porphyromonas gingivalis, Porphyromonas endodontalis, and Treponema denticola were detected in all patients of both groups before treatment (100% detection level), indicating the high virulence of these red complex periodontopathogens.

Tannerella forsythia was not detected at the beginning of treatment in 7 patients from the control group and 6 patients from the study group. Fusobacterium nucleatum was not detected in 5 patients from the control group (25%), and in 4 patients from the study group (20%), while difference of detection rate was not statistically argumented ($p > 0.05$). Prevotella intermedia was not detected in 5 patients from the control group (25%), and in 4 patients from the study group (20%).

Two weeks after the treatment, the number of periodontopathogens significantly decreased in both groups ($p < 0.05$), reaching a relative norm according to the quantitative assessment algorithm presented in Table 1.

After two months, most pathogens reappeared, but in significantly lower quantities in both groups compared to the situation before the treatment, difference between which was statistically approved both for the study group ($p < 0.05$) and for the control group ($p < 0.05$). No significant differences in the quantitative and qualitative indicators were found between study and control groups at different time points after treatment ($p > 0.05$), nor did any specifically different patterns of changes were registered regarding Fusobacterium nucleatum, Tannerella forsythia, and Prevotella intermedia either in study group or in control group.

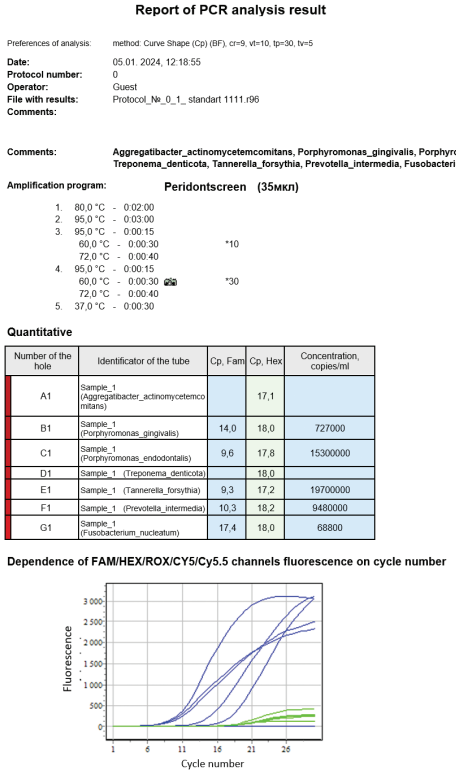
However, it is important to note that at the beginning of the study, Aggregatibacter actinomycetemcomitans was not detected in 40% of patients in the control group, and in 45% patients in the study group. However, two weeks after treatment it was not detected at all in 75% of patients in the control group and 80% in the study group. After two months, Aggregatibacter actinomycetemcomitans reappeared, although in smaller quantities, in 90% of patients in the control group, however, in the study group, among patients in whom Aggregatibacter actinomycetemcomitans was not detected after two weeks, it remained undetectable even after two months. Overall, Aggregatibacter actinomycetemcomitans was identified in only 20% of the patients in the second group after two months.

Treponema denticola was detected in 90% of patients in both groups before treatment. After two weeks, its quantity нaы significantly decreased: it was not detected in 60% of patients in both groups. However, after two months Treponema denticola was detected in all patients in the first group (100% detection level), although in significantly lower quantities compared to situation before treatment ($p < 0.05$). However, in the second group, it remained undetectable in 75% of patients after two months, (including 100% of those in whom it was already absent two weeks after treatment).

It was also revealed that periodontopathogens that were not detected in specific subjects in both groups before treatment remained undetectable after two weeks and two months after the treatment, however, only 3 patients were characterized with such feature (1 in study group, and 2 in control group).

Porphyromonas gingivalis (Pg) and Porphyromonas endodontalis (Pe), these pathogens were detected in 100% of patients in both groups before treatment, in high quantities. Their presence persisted in both groups after two weeks and two months, but in significantly lower quantities ($p < 0.05$). No significant difference in the average quantitative levels of Porphyromonas gingivalis and Porphyromonas endodontalis between the two groups were observed at different time points ($p > 0.05$).

Examples of PCR real-time samples are presented in Figures 1a, 1b, 1c, and 2a, 2b, 2c.



Report of PCR analysis result

Preferences of analysis: method: Curve Shape (Cp) (BF), cr=9, vt=10, tp=30, tv=5

Date: 05.01. 2024, 12:18:55
Protocol number: 0
Operator: Guest
File with results: Protocol_№_0_1_ standart 1111.r96
Comments:

Comments: Aggregatibacter_actinomycetemcomitans, Porphyromonas_gingivalis, Porphyromonas_endodontalis, Treponema_denticota, Tannerella_forsythia, Prevotella_intermedia, Fusobacterium_nucleatum

Amplification program: Peridontscreen (35мкл)

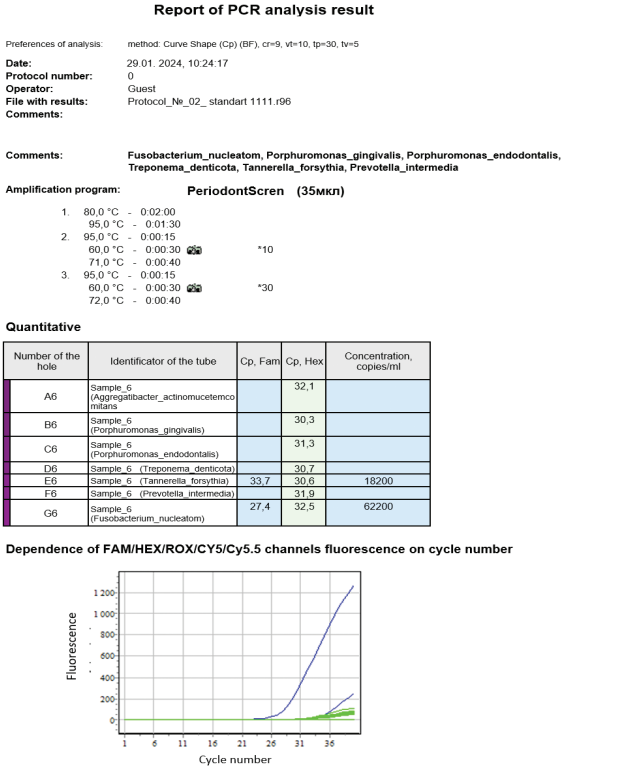
1. 80,0 °C - 0:02:00
2. 95,0 °C - 0:03:00
3. 95,0 °C - 0:00:15
   60,0 °C - 0:00:30 *10
   72,0 °C - 0:00:40
4. 95,0 °C - 0:00:15
   60,0 °C - 0:00:30 *30
   72,0 °C - 0:00:40
5. 37,0 °C - 0:00:30

Quantitative

Number of the hole	Identificator of the tube	Cp, Fam	Cp, Hex	Concentration, copies/ml
A1	Sample_1 (Aggregatibacter_actinomycetemcomitans)		17,1	
B1	Sample_1 (Porphyromonas_gingivalis)	14,0	18,0	727000
C1	Sample_1 (Porphyromonas_endodontalis)	9,6	17,8	15300000
D1	Sample_1 (Treponema_denticota)		18,0	
E1	Sample_1 (Tannerella_forsythia)	9,3	17,2	19700000
F1	Sample_1 (Prevotella_intermedia)	10,3	18,2	9480000
G1	Sample_1 (Fusobacterium_nucleatum)	17,4	18,0	68800

Dependence of FAM/HEX/ROX/CY5/Cy5.5 channels fluorescence on cycle number

Fig. 1a. Result of the analysis of a patient from control group before treatment



Report of PCR analysis result

Preferences of analysis: method: Curve Shape (Cp) (BF), cr=9, vt=10, tp=30, tv=5

Date: 29.01. 2024, 10:24:17
Protocol number: 0
Operator: Guest
File with results: Protocol_№_02_ standart 1111.r96
Comments:

Comments: Fusobacterium_nucleatom, Porphyromonas_gingivalis, Porphyromonas_endodontalis, Treponema_denticota, Tannerella_forsythia, Prevotella_intermedia

Amplification program: PeriodontScren (35мкл)

1. 80,0 °C - 0:02:00
   95,0 °C - 0:01:30
2. 95,0 °C - 0:00:15
   60,0 °C - 0:00:30 *10
   71,0 °C - 0:00:40
3. 95,0 °C - 0:00:15
   60,0 °C - 0:00:30 *30
   72,0 °C - 0:00:40

Quantitative

Number of the hole	Identificator of the tube	Cp, Fam	Cp, Hex	Concentration, copies/ml
A6	Sample_6 (Aggregatibacter_actinomucetemcomitans		32,1	
B6	Sample_6 (Porphuromonas_gingivalis)		30,3	
C6	Sample_6 (Porphuromonas_endodontalis)		31,3	
D6	Sample_6 (Treponema_denticota)		30,7	
E6	Sample_6 (Tannerella_forsythia)	33,7	30,6	18200
F6	Sample_6 (Prevotella_intermedia)		31,9	
G6	Sample_6 (Fusobacterium_nucleatom)	27,4	32,5	62200

Dependence of FAM/HEX/ROX/CY5/Cy5.5 channels fluorescence on cycle number

Fig. 1b. Result of the analysis of a patient from control group 2 weeks after treatment

Report of PCR analysis result

Preferences of analysis: method: Curve Shape (Cp) (BF), cr=9, vt=10, tp=30, tv=5

Date: 06.03 2024, 12:51:03
Protocol number: 0
Оператор: Guest
File with results: Protocol_№_03 standart 1111.r96
Comments:

Тест: **Aggregatibacter_actinomucetemcomitans, Porphuromonas_gingivalis, Porphuromonas_endodontalis, Treponema_denticota, Tannerella_forsythia, Prevotella_intermedia, Fusobacterium_nucleatom**

Amplification program: **PeriodontScren (35мкл)**

1. 80,0 °C - 0:02:00
   95,0 °C - 0:01:30
2. 95,0 °C - 0:00:15
   60,0 °C - 0:00:30 *10
   71,0 °C - 0:00:40
3. 95,0 °C - 0:00:15
   60,0 °C - 0:00:30 *30
   72,0 °C - 0:00:40

Quantitative

Number of the hole	Identificator of the tube	Cp, Fam	Cp, Hex	Concentration, copies/ml
A4	Sample_3 (Aggregatibacter_actinomucetemcomitans)		26,3	
B4	Sample_3 (Porphuromonas_gingivalis)	33,0	26,2	9300
C4	Sample_3 (Porphuromonas_endodontalis)	34,6	26,4	7800
D4	Sample_3 (Treponema_denticota)		26,1	
E4	Sample_3 (Tannerella_forsythia)	34,9	26,0	7600
F4	Sample_3 (Prevotella_intermedia)		26,3	
G4	Sample_3 (Fusobacterium_nucleatom)	37,1	26,3	4800

Dependence of FAM/HEX/ROX/CY5/Cy5.5 channels fluorescence on cycle number

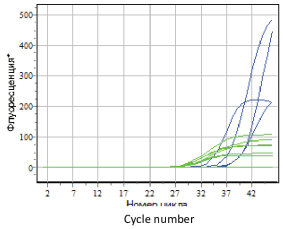


Fig. 1c. Result of the analysis of a patient from control group 2 months after treatment

Report of PCR analysis result

Preferences of analysis: method: Curve Shape (Cp) (BF), cr=9, vt=10, tp=30, tv=5

Date: 1 травень 2024, 11:18:55
Protocol number: 0
Operator: Guest
File with results: Protocol_№_12 standart 1111.r96
Comments:

Тест: **Aggregatibacter_actinomycetemcomitans, Porphyromonas_gingivalis, Porphyromonas_endodontalis, Treponema_denticota, Tannerella_forsythia, Prevotella_intermedia, Fusobacterium_nucleatum**

Amplification program: **Peridontscreen (35мкл)**

1. 80,0 °C - 0:02:00
2. 95,0 °C - 0:03:00
3. 95,0 °C - 0:00:15
   60,0 °C - 0:00:30 *10
   72,0 °C - 0:00:40
4. 95,0 °C - 0:00:15
   60,0 °C - 0:00:30 *30
   72,0 °C - 0:00:40
5. 37,0 °C - 0:00:30

Quantitative

Number of the hole	Identificator of the tube	Cp, Fam	Cp, Hex	Concentration, copies/ml
A3	Sample_3 (Aggregatibacter_actinomycetemco		18,0	
B3	Sample_3 (Porphyromonas_gingivalis)	11,9	18,6	3170000
C3	Sample_3 (Porphyromonas_endodontalis)	11,2	19,0	5110000
D3	Sample_3 (Treponema_denticota)	12,6	18,2	1880000
E3	Sample_3 (Tannerella_forsythia)	9,8	18,4	14100000
F3	Sample_3 (Prevotella_intermedia)	13,3	18,9	1190000
G3	Sample_3 (Fusobacterium_nucleatum)	16,8	18,7	102000

Dependence of FAM/HEX/ROX/CY5/Cy5.5 channels fluorescence on cycle number

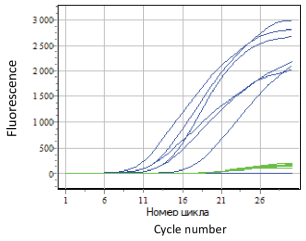


Fig. 2a. Result of the analysis of a patient from study group before treatment

Report of PCR analysis result

Preferences of analysis: method: Curve Shape (Cp) (BF), cr=9, vt=10, tp=30, tv=5

Date: 17 травня 2024, 21:51:03
Protocol number: 0
Operator: Guest
File with results: Protocol_№_01_ standart 1111.r96
Comments:

Comments **Aggregatibacter_actinomucetemcomitans, Porphuromonas_gingivalis, Porphuromonas_endodontalis, Treponema_denticota, Tannerella_forsythia, Prevotella_intermedia, Fusobacterium_nucleatom**

Amplification program: **PeriodontScren (35мкл)**

1. 80,0 °C - 0:02:00
   95,0 °C - 0:01:30
2. 95,0 °C - 0:00:15
   60,0 °C - 0:00:30 *10
   71,0 °C - 0:00:40
3. 95,0 °C - 0:00:15
   60,0 °C - 0:00:30 *30
   72,0 °C - 0:00:40

Quantitative

Number of the hole	Identificator of the tube	Cp, Fam	Cp, Hex	Concentration, copies/ml
A4	Sample_4 (Aggregatibacter_actinomucetemcomitans)		29,2	
B4	Sample_4 (Porphuromonas_gingivalis)	33,8	29,0	380000
C4	Sample_4 (Porphuromonas_endodontalis)	36,3	28,5	48000
D4	Sample_4 (Treponema_denticota)			
E4	Sample_4 (Tannerella_forsythia)	37,8	28,9	18000
F4	Sample_4 (Prevotella_intermedia)	39,1	28,6	5960
G4	Sample_4 (Fusobacterium_nucleatom)		24,0	

Dependence of FAM/HEX/ROX/CY5/Cy5.5 channels fluorescence on cycle number

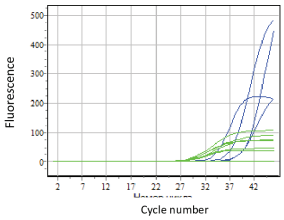


Fig. 2b. Result of the analysis of a patient from study group 2 weeks after treatment

Report of PCR analysis result

Preferences of analysis: method: Curve Shape (Cp) (BF), cr=9, vt=10, tp=30, tv=5

Date: 04 липня 2024, 11:34:00
Protocol number: 0
Operator: Guest
File with results: Protocol_№_0_5_ standart 1111.r96
Comments:

Comments: **Aggregatibacter_actinomucetemcomitans, Porphuromonas_gingivalis, Porphuromonas_endodontalis, Treponema_denticota, Tannerella_forsythia, Prevotella_intermedia, Fusobacterium_nucleatom**

Amplification program: **PeriodontScren (35мкл)**

1. 80,0 °C - 0:02:00
   95,0 °C - 0:01:30
2. 95,0 °C - 0:00:15
   60,0 °C - 0:00:30 *10
   71,0 °C - 0:00:40
3. 95,0 °C - 0:00:15
   60,0 °C - 0:00:30 *30
   72,0 °C - 0:00:40

Quantitative

Number of the hole	Identificator of the tube	Cp, Fam	Cp, Hex	Concentration, copies/ml
A1	Sample_1 (Aggregatibacter_actinomucetemcomitans)		29,5	
B1	Sample_1 (Porphuromonas_gingivalis)	38,2	29,1	2680
C1	Sample_1 (Porphuromonas_endodontalis)	32,0	29,3	35000
D1	Sample_1 (Treponema_denticota)		28,0	
E1	Sample_1 (Tannerella_forsythia)	29,6	29,7	323000
F1	Sample_1 (Prevotella_intermedia)	26,6	30,0	800500
G1	Sample_1 (Fusobacterium_nucleatom)		29,1	

Dependence of FAM/HEX/ROX/CY5/Cy5.5 channels fluorescence on cycle number

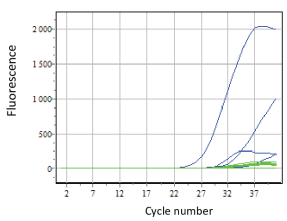


Fig. 2c. Result of the analysis of a patient from Group 2 2 months after treatment

Responses obtained from questionnaire regarding organoleptic features of mouthwashes containing either chlorhexidine or active oxygen revealed that patients did not notice significant differences in the tastes of both mouthwashes itself, but 15% of the patients from the control group evidenced unpleasant symptoms, such as staining and taste disturbances, after two weeks of usage. Patients from the study group that were using oxygen-releasing mouthwash did not notice any unpleasant symptoms two weeks after hygiene aid use. 90% of patients from the study group also noticed that present mouthwash with oxygen-releasing feature was better than one they used before, while 65% from the control group answered that chlorhexidine-based mouthwash used in present study was not better compared to one they have used before (Figure 3).

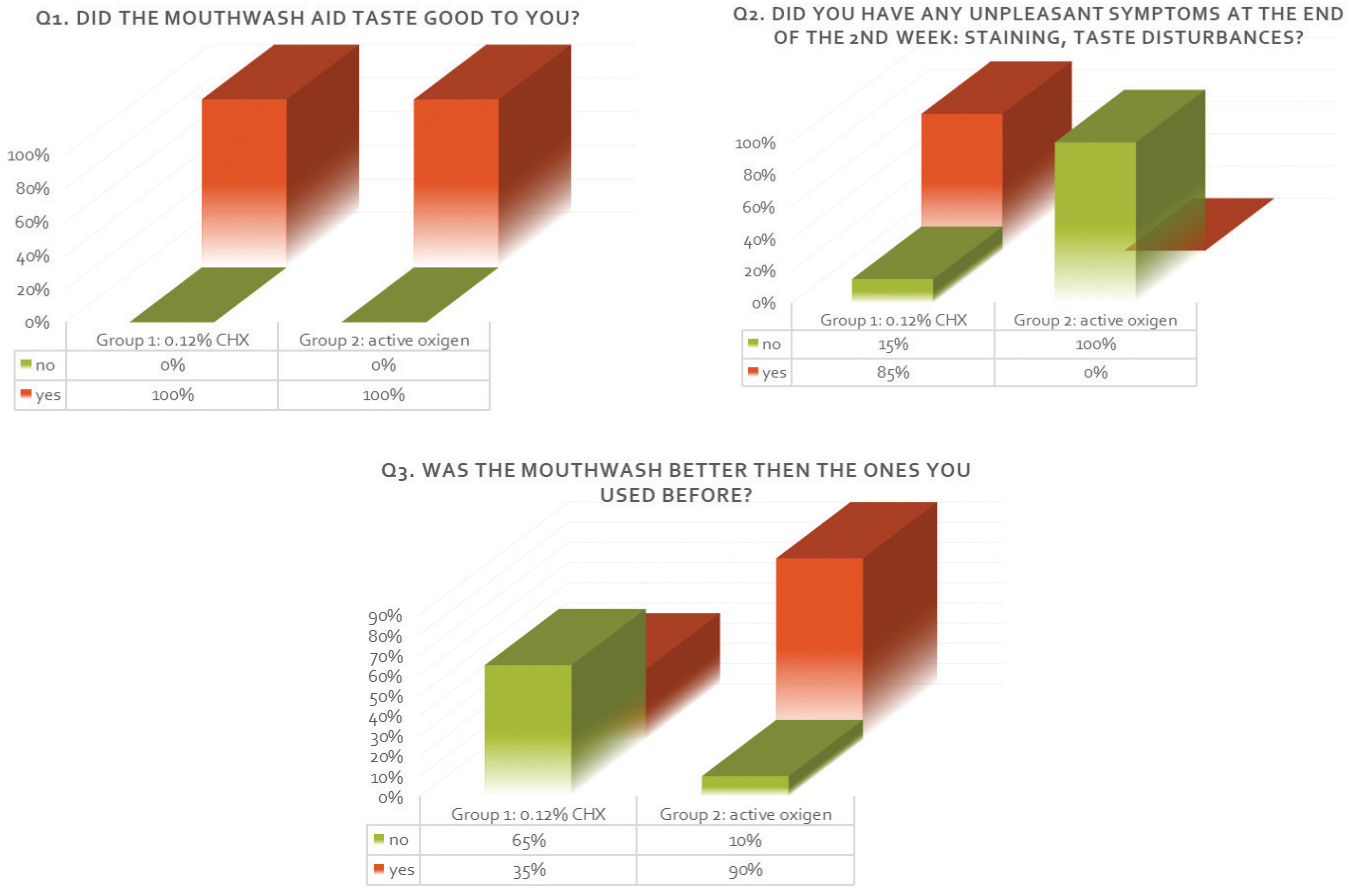


Fig. 3. Evaluation of the organoleptic properties of mouthwashes containing chlorhexidine and active oxygen. The survey was conducted two weeks after application

Discussion

Considering obtained results of present study, which demonstrated analogical pattern of changes for Fusobacterium nucleatum, Tannerella forsythia, Prevotella intermedia, Porphyromonas gingivalis and Porphyromonas endodontalis among study and control groups, but differences regarding Aggregatibacter actinomycetemcomitans and Treponema denticola in means of detection rates noticed among study and control groups especially at two months period after provided treatment, it may be resumed that formulated null hypothesis may be partially rejected. Generally, both chlorhexidine-based and active oxygen-based products demonstrated good antimicrobial activity at various stages of treatment.

Local delivery of the drugs into the periodontal pocket characterized with the number of advantages compared to the systematic drug delivery, one of which is direct contact of active substance with surrounding periodontal tissues while also minimization of systematic effect of different substances [29, 30]. Direct contact of locally delivered drug promotes its faster and improved effect, while form of delivery may be represented by periodontal chips, gels, intrapocket irrigation solutions, ointments and mouthwashes [29, 30]. Even though different chlorhexidine formulation has been used previously in periodontal practice, new agents with specific target advantages have been presented, efficiency and usage reasonability of which undergoes now through laboratory and clinical validation [31]. One of the most promising representatives of locally delivered agents in periodontics are such with oxygen-releasing effect [16, 17, 18, 32, 33]. Topical oxygen therapy supports and promotes periodontal tissue healing after different periodontal interventions, while also prevents infection development, improves processes of reepithelialization, collagen production and angiogenesis [33, 34]. Important advantage of local oxygen therapy is that it's not causing development of microbial resistance considering broad-effect oxidation action.

Several previously published clinical case reports have demonstrated effectiveness of using topical oxygen-releasing agents through the course of gingivitis or periodontitis treatment [18, 33, 34]. But effectiveness of such was also approved by several randomized and prospective clinical and clinico-microbiological studies.

In the split-mouth study of Singh A. et al it was proved that additional usage of oxygen-releasing gel installed within periodontal pocket after SRP procedure provided statistically approved benefit in means of changes within periodontal pocket depth, clinical attachment level and bleeding on probing compared to the solely realization of SRP without usage of any additional local drug [19]. Garcia C. et al. also demonstrated that application Blue®M gel together with SRP characterized with better clinical improvement than SRP procedure alone [35]. Application of Blue®M inhibited

bone resorption and inflammation to greater extent compared to SPR group, but effect of such was lesser compared to targeted photodynamotherapy [35].

Another split-mouth randomized clinical study held among dental patients with generalized bleeding on probing and periodontal pocket with more than 5 mm depth demonstrated that patients who received application of oxygen-releasing gel within periodontal pocket after SRP in 3 months demonstrated greater tendency to the pocket depth reduction compared to the patients who received chlorhexidine gel intra-pocket installation with the same purpose [35].

Previous randomized clinical trial of split-mouth design demonstrated that local application of oxygen-releasing gel into the periodontal pocket after provided scaling and root planning demonstrated significantly better improvement in means of periodontal pocket depth, clinical attachment level and wound healing index in comparison to usage of 0.2% chlorhexidine gel with the same purpose [36]. It is worth noting that in the same study authors found no difference between application of either oxygen-releasing gel or chlorhexidine gel in means of gingival index and plaque index improvements at the 3 months control assessment after the scaling and root planning combined with local intra-pocket drug delivery [36].

In the prospective clinical study held among patients with II stage periodontitis treated with SRP and local drug delivery it has been shown that scenario of SRP combined with oxygen-releasing gel demonstrated greater capability to reduce values of gingival index, probing depth, clinical attachment loss, while also to decrease total oxidant status and oxidative stress index, and increase total antioxidant capacity compared to the outcome registered after SRP combined with intra-pocket chlorhexidine gel application [37]. Above mentioned findings may be used to suggest that oxygen-releasing agents provide better potential to re-establish oxidant-antioxidant imbalance, which is developing within oral cavity due to the periodontitis pathology.

Another split-mouth randomized controlled trial highlighted that the usage of oxygen-releasing gel may be beneficial at the sites where the access to the base of periodontal pocket may be complicated as an alternative to the chlorhexidine gel [38]. Agarwal S. et al. also noted that the periodontal pocket depth reduction and clinical attachment re-establishment were greater when SRP was combined with oxygen-releasing gel as local drug compared to chlorhexidine gel. In the randomized controlled study authors also noted that P. gingivalis count within the subgingival plaque samples was statistically lower in group where oxygen-releasing gel was used as adjunct local agent compared to control group where chlorhexidine gel was used with the same purpose [38]. Our study on the other hand demonstrated significant reduction of Porphyromonas gingivalis bacterial load after application of Blue®M oxygen-releasing agent, but such changes were analogical to cases with chlorhexidine application. It is worth noting that in present study analysis of all major periodontal pathogens was held, and detection rate's reduction for Aggregatibacter actinomycetemcomitans and Treponema denticola was significantly greater in scenarios of using oxygen-releasing agent than chlorhexidine-based agent as topical intrapocket medication.

Within the clinic-microbiological study of Koul A. it was found that application of Blue®M gel into the periodontal pockets after SRP support reduction of colony forming units of Porphyromonas gingivalis and Aggregatibacter actinomycetemcomitans assessed semiquantitatively, but such reduction was comparatively lower compared to the application of chlorhexidine gel with the same purpose [16]. However, considering that Bluem® gel group demonstrated analogical reduction within gingival index and periodontal pocket depth compared to the chlorhexidine group it was concluded that impact of above-mentioned agents is coequally effective [16]. In our study partially analogical results were obtained, because pattern of changes for Porphyromonas gingivalis was the same between study and control groups, but regarding Aggregatibacter actinomycetemcomitans controversial tendency was observed, because patients supported with intrapocket oxygen-releasing agent application were characterized with greater reduction in detection level compared to control group. Such inconsistencies between studies could be argumented by the fact that in Koul's study CFU was targeted criteria for investigation by culturing methodology, while in present study PeriodontScreen PCR-approach was used.

In clinico-microbiological study of Agarwal R. it was found that treatment modalities with combination of SRP procedure either with oxygen-releasing gel or chlorhexidine gel provides better improvements of clinical parameters, including gingival index, periodontal pocket depth and clinical attachment level compared to the stand-alone procedure of scaling and root planning [39]. Also, both agents were equeally affective in significant reduction of red complex bacteria (Porphyromonas gingivalis, Treponema denticola, and Tannerella forsythia) microbiological count [39]. Even though differences in microbiological count of Porphyromonas gingivalis, Treponema denticola, and Tannerella forsythia between SRP combined with oxygen-releasing gel and SRP combined with chlorhexidine gen were not statistically significant, but in-detailed analysis of results revealed that oxygen-releasing modality was characterized with greater levels of above-mentioned bacteria reduction. In present study decreasing detection rate of Treponema denticola was noted with more pronounced manner among group of patients treated with the use of oxygen-releasing agent than in group of subjects treated with chlorhexidine intrapocket applications additionally to standard SRP procedures.

Pilot study of Deliberador et al. demonstrated that within laboratorial conditions Blue®M oral gel demonstrated inhibitory halo effect against Porphyromonas gingivalis and such was relatively analogical to the effect obtained by chlorhexidine if dose concentration of Blue®M oral gel was kept at 75-100% range [15]. In present study changes of Porphyromonas gingivalis detection rates were similar between study and control group with generalized tendency to the reduction on the background of provided SRP combined either with oxygen-releasing gel or chlorhexidine gel.

Usage of oxygen-releasing agent was described not just solely for the non-surgical periodontal aims, but also as an aid to the different surgical procedures. Julianna H. and Tarek S. demonstrated that oxygen-releasing agents tend to decrease pain symptoms after gingival surgical depigmentation procedure, while also such approach supports wound healing and reepithelization processes [17].

Analysis of different oxygen-releasing agents is still ongoing, demonstrating that by the mechanism of action such could be more effective against green and purple periodontal complexes, while chlorhexidine seems to be more sufficient with the impact on red-complex bacterial proportions and alterations of different bacterial complexes ratio [40]. Moreover, recent study on cytotoxicity of oxygen-releasing agents was held demonstrating analogical apoptosis rates for oral human fibroblasts under the influence of chlorhexidine and Blue®M, while also representing and differences of such agents in means of keratinocytes apoptosis rates and capacities of wound closure within the scratch assay [12].

Most of studies dedicated to the clinical assessment of oxygen-releasing gels used in complex of periodontal treatment characterized with relatively low study sample sizes, which in turn causing limitation for further generalization of obtained results. Also, most of such studies are characterized with short term monitoring period within the range of 3-6 months, which makes it hard to objectify durability of treatment effects after oxygen-releasing gel application. There is still deficiency of studies targeted at assessment of bacteriological parameters changes under the conditions of using oxygen-releasing agents, such as Blue®M gel or mouthwash in various clinical scenarios of periodontitis treatment.

Limitations of presents study associated with relatively small study sample and short period of monitoring for two months, but such are argumented by the pilot design of clinico-microbiological study on the base of dental clinic located in Ukraine. Also, further studies should be aimed at providing in-detail analysis of periodontal pathogens concentrations and fluctuations of their bacterial loads through the longer period of monitoring among greater number of patients, while present study focused on detection rates and factual differences in parameters established for groups of patients treated either with oxygen-releasing gel or chlorhexidine-containing gel.

Conclusions

Considering limitation of present study, provided analysis of the obtained data revealed that oxygen-based preparations exhibit antibacterial properties no less effective than CHX-based preparations, which allows to recommend such as additional treatment modalities for local application and home hygiene aid during complex treatment of patients with periodontitis. Taking into account registered detection levels changes after provided treatment it may also be assumed that oxygen-releasing gel demonstrated the most pronounced antibacterial properties against such pathogens as Aggregatibacter actinomycetemcomitans and Treponema denticola, particularly in 2 months long monitoring.

However, further large-scale studies are needed to confirm these findings in definitive manner. When comparing overall patient feedback on the organoleptic properties and side effects of the studied preparations, it was observed that the hygiene products offered to both groups have pleasant taste qualities. However, oxygen-based preparations do not cause side effects in 100% of cases and do not induce unpleasant sensations during their use, unlike CHX-based preparations. Some patients experienced tongue and cervical tooth staining, as well as slight taste alterations by the end of the second week of chlorhexidine-based aids usage.

Conflict of Interest

Authors do not have any potential conflict of interests that may influence the decision to publish this article.

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Вплив киснево-вивільняючих речовин та підтримуючих гігієнічних засобів на мікробіоту пародонтальних кишень під час лікування пацієнтів з пародонтитом III-IV стадії: клініко-мікробіологічне дослідження

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A – розробка концепції та дизайну дослідження, B - збір та або систематизація даних дослідження, C - аналіз та тлумачення даних дослідження, D - написання публікації, E - критичне доопрацювання тексту публікації, F- остаточне затвердження.

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Анотація

Вступ. З огляду на те, що засоби, які вивільняють кисень, є відносно новими у пародонтологічній практиці, видається клінічно доцільним оцінити, яким чином їх застосування може впливати на результати класичних методів лікування пародонтиту, якщо останні модифікуються шляхом додаткового використання активних кисневмісних речовин як локального терапевтичного засобу. Крім того, вплив кисневивільняючих сполук у пародонтології потребує кількісного визначення не лише за змінами клінічних показників, але й за динамікою мікробіологічних параметрів, зареєстрованих із застосуванням точних лабораторних методів.

Мета. Надати порівняльну кількісну оцінку змін мікробіоти пародонтальних кишень у пацієнтів із пародонтитом III–IV стадії після модифікації стандартних методик скейлінгу та згладжування коренів шляхом застосування гелю, що вивільняє кисень, у поєднанні з допоміжними гігієнічними засобами, та порівняти ефективність такого підходу з дією засобів, що містять хлоргексидин.

Матеріали та методи. Пацієнти з пародонтитом III–IV стадії були рандомізовано розподілені на контрольну та досліджувану групи в співвідношенні 1:1 по 20 осіб.. Незалежно від розподілу всі пацієнти пройшли базове нехірургічне пародонтологічне лікування відповідно до протоколів Європейської федерації пародонтології (EFP), яке включало суб'ясенну інструментальну обробку. Пацієнти контрольної групи, окрім базового нехірургічного пародонтального лікування, одразу після очищення отримували постінструментальне внесення гелю, що містить хлоргексидин, у пародонтальні кишені. Пацієнти в досліджуваній групі, окрім базового нехірургічного пародонтального лікування отримували внесення гелю, що вивільняє кисень, який також вводили безпосередньо у пародонтальні кишені одразу після під'ясенної інструментальної обробки. Мікробіологічну оцінку біотопу пародонтальних кишень проводили за допомогою ПЛР тесту PeriodontScreen Real-time. Зразки для дослідження були відбирані у три часові проміжки: до початку лікування, через два тижні після лікування та через два місяці після лікування.

Результати. Через два місяці після лікування Aggregatibacter actinomycetemcomitans знову виявляли у 90% пацієнтів контрольної групи, хоча й у менших кількостях. Проте в досліджуваній групі серед пацієнтів, у яких Aggregatibacter actinomycetemcomitans не був виявлений через два тижні після лікування, його відсутність зберігалася навіть через два місяці. Загалом, через два місяці після лікування Aggregatibacter actinomycetemcomitans було виявлено лише у 20% пацієнтів другої (досліджуваної) групи. Статистично значущої різниці в середніх кількісних рівнях Porphyromonas gingivalis та Porphyromonas endodontalis між двома групами в різні періоди часу не виявлено ($p > 0,05$).

Висновки. З урахуванням обмежень даного дослідження, проведений аналіз отриманих даних показав, що препарати на основі активного кисню виявляють антибактеріальні властивості, не менш ефективні, ніж засоби на основі хлоргексидину. Це дає підстави рекомендувати їх як додаткові лікувальні засоби для локального застосування та підтримки

гігієни порожнини рота під час комплексного лікування пацієнтів із пародонтитом. Зважаючи на зареєстровані зміни рівнів виявлення мікроорганізмів після проведеного лікування, можна також припустити, що гель, який вивільняє кисень, продемонстрував найвираженіші антибактеріальні властивості щодо таких патогенів, як Aggregatibacter actinomycetemcomitans та Treponema denticola, особливо за результатами двомісячного моніторінгу.

Заява про конфлікт інтересів

Автори не мають потенційного конфлікту інтересів, який може вплинути на рішення про публікацію цієї статті.

Заява про фінансування

Не було отримано жодного фінансування для допомоги в підготовці та проведенні цього дослідження, а також у написанні цієї статті.

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