Efficiency of photodynamic therapy in the treatment of peri-implantitis – A three-month randomized controlled clinical trial

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SUMMARY
Introduction Peri-implantitis is an inflammatory lesion of peri-implant tissues. Eradication of the causative bacteria and decontamination of the implant surface is essential in achieving predictable and stable clinical results. Photodynamic therapy (PDT) is non-invasive adjuvant therapeutic method to surgery in the treatment of bacterial infection.

Objective The aim of this study was to evaluate early clinical and microbiological outcomes of peri-implantitis after surgical therapy with adjuvant PDT.

Methods Fifty-two diagnosed peri-implantitis sites were divided into two groups. PDT was used for decontamination of implant surface in the study group; in the control group, chlorhexidine gel (CHX) followed by saline irrigation was applied. Several clinical parameters were recorded before the treatment (baseline values) and three months after surgical treatment. Samples for microbiological identification were collected before therapy, during the surgical therapy (before and after decontamination of implant surface), and three months thereafter, and analyzed with identification systems using biochemical analysis.

Results The use of PDT resulted in significant decrease of bleeding on probing in comparison to CHX (p < 0.001). It showed significant decontamination of implant surfaces with complete elimination of anaerobic bacteria immediately after surgical procedure and three months later.

Conclusion The results indicate that PDT can be used as an adjuvant therapy to surgery for decontamination of implant surface and surrounding peri-implant tissues within the treatment of peri-implantitis.

Keywords: peri-implantitis; decontamination; photodynamic therapy

INTRODUCTION

Peri-implantitis has been defined as an inflammatory process that affects the supporting marginal bone around an implant in function and results in bone resorption [1, 2]. It has been shown that the biofilm formed around osseointegrated implant has an important role in initiation and progression of peri-implant diseases [3, 4]. Most common microorganisms that are related to peri-implantitis are anaerobic bacteria, such as Prevotella intermedia, Porphyromonas gingivalis, Aggregatibacter actinomycetemcomitans, Bacteroides forsythia, Treponema denticola, Prevotella nigrescens, Peptostreptococcus spp., Fusobacterium nucleatum. Some authors suggested that Staphylococcus aureus and Candida albicans may be connected with initiation of peri-implantitis [3, 5]. Excessive mechanical stress, residual cement, poor plaque control could be among risk factors in the onset and development of peri-implantitis [2].

Peri-implantitis is a complex disease; therefore, the therapy continues to be a challenge. Surgical therapy of peri-implantitis has been suggested to be superior to non-surgical therapy [6]. Decontamination of implant surface is one of the most important and difficult steps because of the screw-shaped design and roughness where microorganism and their products are incorporated. Many methods have been suggested, such as mechanical (dental curettes, ultrasonic scalers, air-powder abrasive), physical and/or chemical methods (citric acid, chlorhexidine, EDTA), usually combined with local or systemic antibiotics [7–12]. No single protocol has been suggested for solving this problem.

Photodynamic therapy (PDT) can be a new alternative approach for decontamination of implant surfaces combined with mechanical debridement during surgical therapy. It is a non-invasive therapeutic treatment of various infections caused by bacteria, fungi and viruses [13]. PDT has been defined as an oxygen-dependent reaction that occurs by action of low-energy single-frequency light (diode laser) and activation of the photoactive materials (photosensitizer). The photosensitizer is administered onto exposed tissue. It binds and dyes cells. Upon irradiation with light of specific wavelength of laser, photosensitizer undergoes a transition from a low energy ground state to...
an excited singlet state. Subsequently, it may decay back to its ground state, transition high-energy triplet state, which can react with biomolecules such as endogenous oxygen to produce very reactive products, like singlet oxygen. Singlet oxygen has cytotoxic effect through damage of cell membrane and cell wall. Using this therapy, the target bacteria can be destroyed without adverse effect on the implant surface and surrounding peri-implant tissue [14, 15].

Some articles showed that using chlorhexidine (CHX) as adjunctive chemical agent to decontamination, reduced inflammation and microorganisms on the implant surface. Bioadhesive gels with higher concentrations of CHX have shown greater effectiveness in various clinical situations [16, 17]. However, ideal treatment for peri-implantitis is not defined yet. There are no clinical trials showing effects of PDT during surgical therapy of peri-implantitis.

**OBJECTIVE**

The aim of this study was to compare early clinical and microbiological effects of the adjuvant use of PDT to surgical treatment of peri-implantitis, comparing the effects of decontamination of the implant surface to those when 1% CHX gel was used.

**METHODS**

Patients were selected from two dental clinics: Department of Periodontology, University of Belgrade, and Department of Implantology, Military Medical Academy, from January 2014 to February 2015. The research protocol was submitted to and approved by the Ethical Committee, University of Belgrade, Serbia (number 36/28). The study was carried out in accordance with the ethical principles of the World Medical Association Declaration of Helsinki. Before the procedure, all participants were informed about the study and signed a written consent. All participants had to meet the following inclusion criteria: age >18 years, no periodontal or peri-implant treatment three months prior to the study, presence of minimum one implant in function, early or moderate type of peri-implantitis classified by Froum and Rosen [18]. Exclusion criteria were the following: uncontrolled medical conditions, use of systemic antibiotics in the previous six months, pregnancy and lactation, therapy of peri-implantitis in the last three months previously.

**Microbiological samples and analysis**

The first samples for microbiological analysis were taken before any measurements from the deepest peri-implant pockets. After the removal of subgingival plaque, sample sites were isolated with cotton rolls and gently air dried to avoid contamination with saliva. Fine sterile paper points were inserted into the peri-implant pocket until mild resistance and left in place for 30 seconds. The paper points were immediately transferred to the substrate used as multipurpose transport system (ESWAB LQ Amies, COPAN Diagnostics Inc., Murrieta, CA, USA).

The second and third samples were taken separately during the surgical therapy from the implant surfaces. After opening the flap and removing granulation tissue, the second sample was obtained from the implant surface by a transport swab. The swab was immediately transferred to the substrate used as multipurpose transport system (ESWAB LQ Amies, COPAN Diagnostics Inc.). After decontamination using chemical/PDT therapy, the third swab was taken from the implant surface applying the aforementioned procedure.

The samples were inoculated by standard procedures for the diagnosis of anaerobic bacteria. Each sample was inoculated on two blood agars (Columbia agar). One blood agar was incubated at 36.5°C for the diagnosis of aerobic pathogens; the other was incubated at the same temperature in a container for anaerobic diagnostics. Anaerobic conditions in the container were provided by generation bags for anaerobic conditions GENbox anaer (bioMérieux, Marcy l’Etoile, France). Cultivated and isolated anaerobic strains underwent identification process. Identification of isolated strains was reaffirmed by automatic systems of two different manufacturers: BBL Crystal ID Kit for anaerobes (Becton Dickinson, Sparks Glencoe, MD, USA), and VITEK 2 ID ANC (bioMérieux, Marcy l’Etoile, France).

The measurements were done and recorded before any treatment. All measurements were made at the following six sites of the implant with signs of peri-implantitis: mesiobuccal, mid-buccal, distobuccal, mesio-oral, mid-oral, disto-oral by one examiner (DR), using a graduated probe (PCPUNC 15, Hu Friedy, Chicago, IL, USA). The applied probing force was standardized force of 0.25 N. The implant shoulder was used as landmark for calculation of mucosal recession and clinical attachment level. The following clinical parameters were registered:

- Peri-implant probing depth (PPD) – measured in millimeters from the mucosal margin to the bottom of the peri-implant pocket;
- Clinical attachment level (CAL) – measured in millimeters from the implant shoulder to the bottom of the peri-implant pocket;
- Mucosal recession (MR) – calculated as the difference between the CAL and PPD;
- Bleeding on probing (BOP) – evaluated as being present if bleeding was evident within 30 seconds after probing, or absent, if no bleeding was observed;
- Suppuration (SUP) – present or absent.

Clinical parameters were measured and recorded before (baseline values) and three months after therapy. All clinical examinations were performed after removal of the abutments attached to the implants. Fifteen days after therapy the provisional restoration was performed on the treated implants.
Treatment procedure

After clinical parameters were recorded and samples were taken, all the patients underwent a single episode of non-surgical therapy. It implied mechanical method for debridement of implants and remaining dentition in order to reduce signs of inflammation. Instructions for oral hygiene were proposed during the same visit.

Surgical treatment

During the surgical procedure, all the patients were randomly divided into two groups: the study group (PDT group) and the control group (CHX group). Similar methodology procedure was described in a study by De Waal et al. [17].

Surgical treatment of peri-implantitis was performed by one experienced oral surgeon (ZL) two weeks after non-surgical therapy (in accordance with Schwarz et al. [19]). Mucoperiosteal buccal and lingual incisions were made with surgical blade No. 15 under local anesthesia (2% lidocaine with epinephrine, 1:100,000). Flaps were designed to permit optimal access to the peri-implant bone defect for granulation tissue removal and decontamination of the implant surface. Full thickness mucoperiosteal flaps were elevated buccally and lingually. Removal of granulation tissue and mechanical implant surface cleaning were done using graphite curettes (Straumann® Dental Implant System; Straumann AG, Basel, Switzerland).

Decontamination of implant surfaces

In the study group, after careful removal of granulation tissue and mechanical debridement of implant surface, decontamination of implant surfaces and peri-implant tissues was performed using PDT (HELBO, Photodynamic Systems GmbH, Wels, Austria). Photosensitizer, phenothiazine chloride (HELBO® Blue Photosensitizer, bredent medical GmbH & Co. KG), was applied onto implant surface, bone and peri-implant soft tissue, for 3 minutes. Irrigation of photosensitizer was performed with saline, according to instructions of the manufacturer. Implant surface and the surrounding tissue were exposed to the laser light by means of fibers (HELBO® TheraLite Laser HELBO® 2D Spot Probe; Bredent medical GmbH & Co. KG) for 30 seconds/spot, which operates on wave length of 660 nm and irradiance of 100 mW (Figure 1a–f).

In the control group, after removal of granulation tissue, 1% gel of chlorhexidine (Chlorhexamed® – Direkt; GlaxoSmithKline, GmbH & Co. KG, München, Germany) was put on implant surface. One minute after exposing implant surface with CHX, it was irrigated for 1 minute by saline.

Bone augmentation and bio-resorbable membrane were applied in peri-implant defects using artificial bone of bovine origin (Bio-Oss and Bio-Gide; Geistlich Pharma, Wolhusen, Switzerland). The mucoperiosteal flaps were repositioned and sutured [17, 19].

All the patients from both groups were prescribed antibiotics over a five-day period (amoxicillin caps. 500 mg,
three per day). It was recommended that patients don't use mouthwash during the postoperative period.

Followed up period

Three months after therapy samples for microbiological analysis were taken from the reduced peri-implant pockets in the same way described above. In addition, measurements of clinical parameters were recorded as well.

Statistical analysis

Data are presented as mean ± standard deviation or n (%) depending on data type. Chi-squared test, Mann–Whitney U-test, and Student’s t-test were used to assess the differences between the groups. Cochran’s Q-test and Wilcoxon signed-rank test were used to assess significant differences within the groups. All analyses were performed in SPSS Statistics for Windows 20.0 (IBM Corp., Armonk, NY, USA). All p-values less than 0.05 were considered statistically significant.

RESULTS

There were 52 peri-implantitis sites diagnosed in 40 systemically healthy patients, which were treated and re-examined in a three-month period. Demography and clinical description of the study population are shown in Table 1. No adverse events and side effects were reported during and after therapy.

Clinical parameters and outcomes

From a total of 52 treated peri-implantitis sites, 12 peri-implantitis sites belonged to the category of moderate, and 31 to the category of early peri-implantitis, classified by Froum and Rosen [18]. The rest of peri-implantitis instances had depths of ≥ 5 mm in only one peri-implant pocket, as one of the inclusion criteria.

The mean value and standard deviation of PPD and CAL are shown in Table 2. Both groups showed statistically significant reduction of peri-implant pockets (p < 0.001). It has been shown that the greater (but not statistically significant) reduction of PPD was in the study group compared to the controls (p = 0.07). The results of our study showed that there was no statistically significant difference in CAL between the two tested groups three months after the therapy (p = 0.883). Also, there were no statistically significant differences in marginal recession.

In the study group, there was a statistically significant reduction of BOP at all six points compared with the control group three months after the therapy (p < 0.001).

Microbiological outcomes

All cultivated anaerobic microorganisms which were isolated from deepest peri-implant pockets and implant surfaces are shown in Table 3. It was shown that some of these bacteria were isolated only from implant surfaces.
Candida spp. was also isolated from the deepest peri-implant pockets.

The results showed that the amount of anaerobic microorganisms was significantly reduced and in most cases eliminated, after using both anti-infection therapeutic methods during surgery therapy as well as three months after the therapy procedure. It showed significant reduction of anaerobic microorganisms in the study group in comparison with the control group, immediately after decontamination of the implant surface and also three months after therapy (Veillonella spp., p < 0.007). Three months after therapy, Actinomyces naeslundii was only isolated in peri-implant pockets in the control group.

The results of the study show that using chlorhexidine leads to significant reduction of Actinomyces odontolyticus (p < 0.046), Fusobacterium nucleatum (p = 0.23) compared with using photodynamic therapy. The presence of Aggregatibacter actinomycetemcomitans, Tannerella forsythia, and Treponema denticola was not identified.

**DISCUSSION**

The short-term results of the present study show that both examined methods for debridement and decontamination of implant surfaces during surgical therapy (PDT and 1% chlorhexidine gel), significantly improve clinical and microbiological outcomes.

In the current literature, most attention is given to systemic and/or local use of antibiotics or implantoplasty for the decontamination of implant surfaces during surgical procedures [3, 10, 20]. However, these methods showed side effects, as well as bacterial resistance to some drugs and allergic reactions during and after their consumption [10]. It has been recorded that implantoplasty leads to marginal recession, which is disadvantageous in terms of function and aesthetics [2, 20].

Some authors consider PDT to be less harmful and effective solution for the decontamination of the implant surface [13, 14]. This therapy was widely used in nonsurgical therapy of peri-implantitis [15, 21, 22]. It has been suggested that using only photodynamic therapy several times may lead to total recovery [22]. Schwarz et al. [6] suggested that surgical therapy of peri-implantitis has been superior to non-surgical therapy. The explanation lies in the open access and controlled removal of granulation tissue and decontamination of the exposed implant surfaces.

The results of the present study show that there are statistically significant changes in peri-implant probing depth and clinical attachment level measured at baseline and three months after therapy. The depth of peri-implant pockets in both tested groups was reduced approximately 2 mm. Higher reduction of peri-implant pocket depth was in the study group, but without statistical significance. This could be explained by larger baseline levels of peri-implant pockets depth recorded in the study group. It seems that PDT can promote re-osseointegration more rapidly than CHX, without side effects on the bone. The results show significant reduction of BOP and suppuration three months after using PDT. It is known that BOP is one of the most essential and important signs of peri-implantitis; therefore, the use of PDT can achieve elimination of BOP and promote better healing. In the study by De Waal et al. [17], similar methodology was used, but they didn't achieve the significant difference in clinical parameters using two concentration of chlorhexidine solutions (0.12% and 2%) in the examined follow-up periods. These results differ from ours due to improvements of clinical parameters in our study. In the study by Heitz-Mayfield et al. [10], after surgical debridement and implant surface decontamination following by saline irrigation, systemic amoxicillin...
and metronidazole were prescribed. Although clinical results of their study were similar to ours, using adjunct PDT could be efficient, as it leads to lower consumption of antibiotics and antiseptics, without side effects.

Cultivation of anaerobic microorganisms showed the presence of various anaerobes isolated from peri-implant pocket before any treatment, as well as on implant surface before decontamination. Most of these bacteria belonged to the pathogenic microorganisms from red and orange complex described by Socransky et al. [23]. In our study, bacteria of yellow, purple, and green complex were also found, which is assumed to be the first phase of colonization of implant surface. This can also represent a possible bridge for the adherence of bacteria from orange and red complexes in a later phase of colonization and maturation of dental biofilm. The results also showed the presence of *Staphylococcus aureus*. It was mentioned that it can be one of the possible pathogenic microorganisms that promote initiation and progression of peri-implantitis. This bacteria was isolated only from the implant surface, so it can be assumed that this can be a very virulent strain, which can enable the progression of peri-implantitis [24]. The presence of *Candida albicans* could be due to inappropriate oral hygiene. Therefore, *Candida* couldn’t have had an influence on initiation of peri-implantitis, as mentioned in some early papers [2].

In both examined groups, statistically significant reduction of anaerobic microorganisms from the peri-implant pockets was evident in the follow-up period and also from implant surface immediately after decontamination. The results show that application of PDT significantly reduced the amount of bacteria, especially those from the red and orange complex. De Waal et al. [17] achieved reduction of microorganisms from implant surface between groups during a surgical procedure, but results were not as statistically significant as in our study. Our study showed significant reduction of microorganisms after using both anti-infection therapeutic methods of decontamination during surgical therapy. *In vitro* study of Marotti et al. [14] showed significant reduction of anaerobic microorganisms after application of PDT and 0.12% solution of chlorhexidine on anodized implants, which are results similar to ours. Another study showed that using PDT with toluidine blue as a dye can reduce but not eliminate pathogenic microorganisms from implant surfaces (*Prevotella intermedia*, *Porphyromonas gingivalis*) [15]. Presence of these bacteria is one of the most important factors in peri-implantitis progression. In contrast, our study has shown elimination of these bacteria. The reason for these differences could be the composition of photosensitizer. Phenothiazine chloride might have greater ability to bind different microorganisms compared to toluidine blue.

In the control group, chlorhexidine gel was chosen for decontamination because of its widely spread use as an antiseptic in different therapeutic procedures. It might be capable of adhering to implant surface. The results show statistically significant reduction of *Fusobacterium nucleatum* and *Actinomyces odontolyticus* after using 1% of CHX in adhesive gel, which can be explained by high concentration and viscosity of CHX in the gel. Although earlier studies described that CHX has a bactericidal effect on microorganisms regardless of the concentration [17], it seems that CHX cannot remove dental biofilm, which can lead to renewed adherence of microorganism and reappearance of inflammation. Similarly, in the control group, the results of the present study showed the reduction of BOP, as one of the signs of inflammation, of only 50%, which confirmed the earlier assumption.

**CONCLUSION**

Even with limitations of the present study, such as short observation period, it can be concluded that photodynamic therapy achieves significant reduction of microorganisms from implant surface and peri-implant tissue when compared with chlorhexidine application, without adverse and side effects on implants and surrounding tissue. Therefore, PDT could be suggested as a new strategy for decontamination of implant surface during surgical treatment of peri-implantitis.

**ACKNOWLEDGEMENT**

This study was partly supported by the Ministry of Education, Science and Technological Development of the Republic of Serbia (project No. 41008).

**REFERENCES**


Процената ефикасности фотодинамске терапије у терапији периимплантитиса после три месеца: рандомизирана контролисана клиничка студија

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КРАТАК САДРЖАЈ
Увод Перимплантитис је инфламаторни процес који захвата механику и потпорну кост окружених имплантата. Елиминација патогених микроорганизама и детоксикација имплантних површина у оквиру терапије периодонтита покренуће је шећерове спале и потпорну кост око осеоинтегрисаног имплANTA. Елиминација патогених микроорганизама и детоксикација имплантних површина коришћен је хлорхексидин гел (CHX) хлорхексидин у гелу (CHX гел) као помоћно терапијско средство за деконтаминацију имплантних површина. Фотодинамска терапија (ФДТ) представља додатен неинвазивни корак у постигању стабилних клиничких резултата.

Циљ рада Циљ рада била је процена клиничких и микробиолошких параметара након хируршках интервенција у терапији периимплантитиса уз додатну примену ФДТ. Резултати показују да ФДТ може да се користи као помоћно терапијско средство за деконтаминацију имплантних површина и периимплантитиса у оквиру терапије периимплантитиса.

Кључне речи: перимплантитис; детоксикација; хлорхексидин; фотодинамска терапија; рандомизован хируршки интервенција

Примљен • Received: 09/12/2015  Ревизија • Revision: 20/06/2016  Прихваћен • Accepted: 30/06/2016

doi: 10.2298/SARH1610478R