Photodynamic Therapy and Periodontology

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ABSTRACT

This review highlights the importance of photodynamic therapy in periodontology. It can be confirmed that the photodynamic therapy as adjunct to classical scaling and root planing can be recommended as treatment option, which can by no means replace the classical therapy concepts. But even over an observation period of six months a slightly higher improvement of the clinical parameters was achieved than with SRP alone. (J Bagh Coll Dentistry 2016; 28(2):69-72).

INTRODUCTION

Periodontal disease caused by dental plaque is characterized by the clinical signs of inflammation and loss of periodontal tissue support. The mechanical removal of this biofilm and adjunctive been the conventional methods of periodontal therapy [(1)]. But the removal of plaque and the reduction in the number of infectious organisms can be impaired in sites with difficult access. The possibility of development of resistance to antibiotics by the target organism has led to the development of a new antimicrobial concept with fewer complications. Photodynamic therapy (PDT) involves the use of low power lasers with appropriate wavelength to kill micro organisms treated with a photosensitizer drug [(2)].

PDT could be useful adjunct to mechanical, as well as antibiotics in eliminating periopathogenic bacteria. Medical applications of (PDT) include treatment of cancer, psoriasis, actinic keratosis, rheumatoid arthritis, age related macular degeneration[(3)]. Broadly, it represents an alternative antibacterial, antifungal, and antiviral approach for drug-resistant organisms including bacteria that grow in the biofilm. Photodynamic therapy (PDT) has emerged in recent years as a non- invasive therapeutic modality for the treatment of various infections by bacteria, fungi, and viruses [(4)].

Photodynamic therapy is defined as an oxygen-dependent photochemical reaction that occurs upon light–mediated activation of a photosensitizing compound leading to the generation of cytotoxic reactive oxygen species; predominantly singlet oxygen[(5)]. It also minimizes the occurrence of bacterial resistance. Photodynamic antimicrobial chemotherapy represents an alternate antibacterial, antifungal, and antiviral treatment against drug-resistant organisms Photo-sensitizer are activated by red light between 630 and 700 nm corresponding to a light penetration depth from 0.5 cm (at 630 nm) to 1.5 cm at (700 nm) which is sufficient for periodontal treatment [(6)].

Sources of this light include arrange of lasers. In present, diode lasers are used predominantly. Non-laser light sources like light emitting diode (LED) and light cure units have tried. An ideal photo-sensitizer should be non-toxic, displaying local toxicity only after activation by illumination. Most commonly use photosensitizers include phenothiazine dyes, methylene blue, and toluidine blue. PDT resulted in improved clinical parameters and decrease in Tumor necrosis factor-α (TNF) and the ligand for receptor activator of NF-κB (RANKL) levels when used as a monotherapy in aggressive periodontitis with SRP [(7)].

Principles of photodynamic therapy

The knowledge of the preferred uptake and accumulation of some dyes (mostly porphyrins) into tumor tissues stimulated the introduction of PDT into clinical practice. PDT is based on the principle that a photo activable substance (the photosensitizer) binds to the cell and can be activated by light of a suitable wavelength [(8)]. During this process, free radicals are formed (among them singletoxygen), which then produce an effect that is toxic to the cell. To have a specific toxic effect on bacterial cells, the respective photosensitizer needs to have selectivity for prokaryotic cells.

Although several authors have reported the possibility of a lethal photosensitization of bacteria *in vivo* and *in vitro*, others have pointed out that Gram negative Bacteria species, due to their special cell wall, are largely resistant to PDT(9). By irradiation with light in the visible range of the spectrum the dye (photosensitizer) is excited to its triplet state, the energy of which is transferred to molecular oxygen. The formed product is the highly reactive singlet oxygen

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capable of reacting with biological systems and destroying them. Only the first excited state with energy of 94 kj/mol (22kcal/mol) above the ground state is important, the second excited state does not react.

Light source

PDT requires a sources of light to activate the photosensitizer by exposure to low power visible light at a specific wavelength. Most photosensitizers are activated by red light between 630 and 700 nm, corresponding to a light penetration depth from 0.5 cm to 1.5 cm. This limits the depth of necrosis. The total light dose, dose rates, and the depth of destruction vary with each tissue treated and photosensitizer used [(10)]. Currently, the light source applied in photodynamic therapy are those of helium – neon lasers (633 nm), gallium-aluminum – arsenide diode lasers (630-690, 830 or 906 nm), and argon laser (488-514 nm), the wavelength of which range from visible light to the blue of argon lasers, or from the red of helium-neon laser to the infrared area of diode lasers [(11)]. Recently, non-laser light source, such as light-emitting diodes (LED), has been used as new light activators in PDT. LED devices are more compact, portable, and cost effective compared to traditional lasers [(12)].

Photosensitizers

An optimal photosensitizer must possess photo-physical, chemical, and biological characteristics. Most of the sensitizers used for medical purposes belong to the following basic structure.

1. 1. Tricyclic dyes with different meso-atoms e .g: Acridine orange, proflavine, riboflavin, methylene blue, fluorescein, and erythrosine[(13)].
2. Tetrapyrroles. E.g.: Porphyrins and derivatives, chlorophyll, phylloerythrin, and phthalocyanines.
3. Furocoumarins. E.g.: Psoralen and its methoxyderivatives,
4. Xanthotoxin, and bergaptene. Photofrin and hematophyrin derivatives are referred to as first generation sensitizers. Second generation photosensitizers include 5-aminolevulinic acid (ALA), Benzoporphyrin derivative, texaphyrin, and temoporfin (mTHPC). These photosensitizers have greater capability to generate singlet oxygen. Topical ALA have been used to treat pre-cancer conditions, and basal and squamous cell carcinoma of skin [(14)].

Comparison between scaling-root-planing (SRP) alone and SRP/photodynamic therapy: six-month study. A total of 22 adults, aged 38 to 74 years, presented as out patients to the Department of Operative Dentistry of the University Medical Center, Johannes Gutenberg University Mainz. All patients (10 = female ; 12 = male) were diagnosed with chronic periodontitis, with four teeth having at least one site with a probing depth of five mm, and presence of bleeding on probing (BOP). The subjects were informed in detail about the aim and course of the study and gave written informed consent. The approval of the course of the study by the ethics commission. Criteria for exclusion from the present study were: presence of a systemic disease, treatment with antibiotics within the last six months, pregnancy, and smoking. For inclusion in the study, the patients had to have at least four teeth with a probing depth of $\geq$ 5 mm. In addition, a good patients' compliance was required, which was monitored over the course of the study by means of measuring plaque and gingival indices. At the beginning of the study, two types of therapy were selected: scaling and root planning (SRP) or SRP and photodynamic therapy (SRP + PDT). For each patient, it was decided by means of a randomization list, which tooth receives which type of therapy. The treatment was done according to a "split mouth design", so that in each patient two teeth belonged to the control group (SRP) and two to the test group (SRP + PDT). All subsequent examinations were done by the same examiner with a fixed periodontal probe (PCP 12, Hu-Friedy, Chicago, IL, USA). All patients received a professional tooth cleaning three weeks prior to the treatment begin. The measurements of the clinical parameters were performed at baseline (one week before treatment), and one month, three and six months after treatment.

Clinical parameters

At each visit, probing depths, absence or presence of bleeding on probing (BOP), gingival recessions and clinical attachment levels at six sites per tooth (buccal; mesiobuccal; distobuccal; lingual; mesiolingual; distolingual) were recorded by the examiner. The examiner was not involved in the therapy, and therefore didn't know which tooth had received which type of therapy (single blinded). To assess the patients' compliance, the gingival index and the plaque index were determined in addition.

Course of treatment

Scaling and root planing was performed in all 22 patients by the same examiner with hand instruments (Gracey curettes, Hu-Friedy, Chicago, IL, USA). Teeth belonging to the test group received a photodynamic therapy in addition. For the photodynamic therapy0.005% methylene blue was used as photosensitizer and activated with a laser [Periowave, Ondine Biopharma, Vancouver, Canada] at a wavelength of 670 nm and a maximum power of 150 mW for 60 seconds. All patients were assessed again by the same examiner at recall visits one month, three and six months after treatment.

Statistical analysis

The statistical analysis of the data was performed in collaboration with the institute of medical biostatistics, epidemiology and informatics of the university medical center of the Johannes Gutenberg university using the program SPSS for medical statistics (17.0 for Windows, Chicago, IL, USA). Descriptive statistics were calculated, and values are given as means ± SD or are shown as boxplots

A descriptive analysis of the gain in clinical attachment and the improvement in probing depths was performed. Comparisons were made for the two different treatments (SRP or SRP + PDT), using as nonparametric test the Wilcoxon test for paired samples. The significance level was set at $p \leq 0.05$.

RESULTS

All subjects enrolled in the present study as outpatients, with a mean age of 59.3 years (SD: 11.7 years), could be examined as planned one month, three and six months after the end of the periodontal treatment. In each case, the chronic periodontitis could be treated successfully by means of the two different therapy concepts using a split mouth design, as it had been explained to the patients. No undesirable effects were observed, and both therapies were tolerated well by the patients. Both lead to a significant reduction in the number of teeth positive when tested for bleeding on probing (BOP), showed high scores for the plaque index; 73% of the patients had a score of 3.

One month after the treatment, considerably lower plaque index scores were determined for both therapy forms. After three months, 77% of the teeth treated with SRP alone had low scores of 0 or 1for the plaque index, and after the combined therapies of SRP and PDT, in 82% of the teeth scores of 0 or 1 were found for the plaque index.

After six months, a slight increase in the plaque index scores was observed; however, independent of the type of treatment, in none of the cases a high plaque index score of 3 was determined. Similar results were found with regard to the measurements of the clinical attachment levels (CAL) over a period of six months. At baseline, the CAL measured 7.2 ± 1.2 mm (SRP) or 8.1 ± 1.3 mm (SRP +PDT). Both therapies lead to a recognizable improvement of the CAL values, with the combined therapy achieving a slightly higher gain in clinical attachment.

At the end of the observation period (six months), there was a clear difference in the effect of the two therapies ($p = 0.052$). At baseline, the probing depth was 5.9 ± 0.8 mm (SRP) or 6.4 ± 0.8 mm (SRP/PDT). Both after the treatment with SRP alone, and with the combined treatment with SRP, followed by photodynamic therapy (PDT), a clear improvement in the measured probing depths was observed over an observation period of six months. After four weeks for SRP therapy alone a mean reduction of the pocket depths by 1.3 ±0.4 mm, and for the combination therapy of SRP+ PDT a mean decrease in the probing depths of 1.5 ± 0.6 mm was found. However, after an observation period of six months, the combined therapy SRP+PDT showed that the mean reduction in probing depths of 2.9 ± 0.8 mm statistically significant improvement ($p = 0.007$), in comparison to therapy alone (2.4 ± 0.6 mm).

Advantage of PDT

1. Minimally invasive technique with least collateral damage to normal cell enhances results and superior healing.
2. Exceedingly efficient broad spectrum of action, since one photosensitizer act on bacteria, virus, fungi, yeasts and protozoa.
3. Efficacy independent of antibiotic resistance pattern of a given microbial strain.
4. The therapy also causes no adverse effect such as ulcers, sloughing or charring of oral tissue.
5. Lesser chance of recurrence when used in treatment of malignancy.
6. Economical to use.

Limitation of PDT

Systemic administration of photosensitizer causes a period of residual skin photosensitivity due to accumulation of photosensitizer under the skin. Therefore photosensitizer can be activated by daylight and cause first and second degree of burns. Hence, direct exposure to sunlight should be avoided for several hours until the drugs completely eliminated from the body.

In conclusion, antimicrobial PDT seems to be a unique and interesting therapeutic approach towards periodontal and endodontic therapy. The numerous *in vitro* studies have clearly demonstrated the effective and efficient bactericidal effect of PDT. However, the superior effects of the adjunctive use of PDT have not been demonstrated clinically or *in vivo* in either periodontal or endodontic therapy. There is a great need to develop an evidence based approach to the use of PDT for the treatment of periodontitis, peri-implantitis, and endodontic therapy. It would be prudent to say that there is an insufficient evidence to suggest that PDT is superior to the tradition l modalities of periodontal therapy. Further, randomized long term clinical studies and meta analyses are necessary to demonstrate the beneficial effect of antimicrobial photodynamic therapy, and in comparison with conventional methods. Antimicrobial photodynamic therapy may hold promise as a substitute for currently available chemotherapy in the treatment of periodontal disease.

In conclusion, it can be confirmed that the photodynamic therapy as adjunct to classical scaling and root planing can be recommended as treatment option, which can by no means replace the classical therapy concepts. But even over an observation period of six months a slightly higher improvement of the clinical parameters was achieved than with SRP alone.

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