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Antimicrobial Photodynamic Therapy: Use and Scope in Periodontology

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ABSTRACT:- Periodontitis is a pathologic manifestation of host response against bacterial challenge that arises from a polymicrobial biofilm at the biofilm and soft tissue of the periodontium interface. This leads to inflammation of the supporting structures, loss of periodontal support and ultimately tooth loss. The main aim of periodontal therapy is removal of biofilm and mechanical removal has been the conventional means for the same. Inherent anatomical complexities in the roots consisting of furcations and concavities especially in deep periodontal pockets, pose a challenge of difficulty in access for the mechanical debridement of the biofilm. Another limitation of mechanical therapy is that some periodontopathogenic organisms like Porphyromonas Gingivalis and Aggregatibacter Actinomycetemcomitans invade the soft tissue and thus recolonisation occurs by these organisms even after mechanical debridement. These problems lead to recurrence of the periodontal infection. Conjunctive use of antibiotics poses a threat of development of resistance. All these challenges led to development of a novel approach as far as periodontal therapy is concerned. A non invasive photochemical approach which involves the use of low level lasers with wavelength appropriate enough to kill microorganisms treated with a photosensitiser drug , called as antimicrobial photodynamic therapy has been developed as a treatment for more optimal and long term treatment for the eradication of periodontopathogenic bacteria in periodontal and peri-implant diseases.

I. INTRODUCTION:

Non biostimulative effect of Low level laser therapy (LLLT) is that it kills bacteria in the presence of suitable photosensitizing agents or dyes. This antimicrobial effect of low – power lasers is called photodynamic therapy. It is also known as photoradiation therapy, phototherapy, antimicrobial photodynamic therapy (aPDT), photodynamic antimicrobial chemotherapy (PACT) or photodynamic disinfection. (DCNA) The use of photodynamic therapy for inactivating microorganisms was first demonstrated more than 100 years ago, when Oscar Raab reported the lethal effect of acridine hydrochloride and visible light on Paramecia caudatum. Photodynamic therapy can selectively target the bacteria without potentially damaging the host tissues.

Photodynamic therapy for human infections is based on the concept that an agent (a photosensitizer) which absorbs light can be preferentially taken up by bacteria and subsequently activated by light of the appropriate wavelength in the presence of oxygen to generate singlet oxygen and free radicals that are cytotoxic to micro-organisms. Photodynamic therapy has emerged as an alternative to antimicrobial regimes and mechanical means in eliminating dental plaque species as a result of pioneering work of Professor Michael Wilson and colleagues at the Eastman Dental Institute, University College London, UK.

MECHANISM OF ACTION OF PHOTODYNAMIC THERAPY

The term 'photodynamic' which is involvement of light and oxygen in the photodynamic process was first demonstrated by Von Tappeiner.

Photodynamic therapy basically involves three nontoxic ingredients:

1. Visible harmless light – visible light of specific wavelength mostly applied in are those of helium-neon lasers (633nm), gallium–aluminum diode lasers (630-690, 830- 906 nm) and argon lasers (488-514 nm).

High level energy laser irradiation is not used to activate the photoactive dye because relatively low level produces high bactericidal effect.

2. Nontoxic photosensitizer – photosensitizers of choice in treatment of periodontitis and peri-implantitis are toluidine blue O and methylene blue.
3. Oxygen.

The mechanism of the action of aPDT is as follows:

A photosensitizer at ground state is activated to a highly energized triplet state by irradiation with light of a certain wavelength. Following irradiation of fluorescent light, photosensitizers may return to their initial state or a higher energy state (triplet state). The dye in triplet state reacts with endogenous oxygen to produce

singlet oxygen or other free radicals and eventually causes selective and quick destruction of the target tissue. The photosensitizers in triplet state react with biomolecules via two mechanisms:

Type I Reaction

Type I reactions involve hydrogen-atom abstraction or electron-transfer reactions between the excited state of the photosensitizer and an organic substrate molecule of the cells, which produces free radicals and radical ions. These free-radical species are generally highly reactive and interact with endogenous molecular oxygen to produce highly reactive oxygen species such as superoxide, hydroxyl radicals and hydrogen peroxide, which are harmful to cell membrane integrity, causing irreparable biological damage.

Type II Reaction

In the Type II, the triplet-state photosensitizer reacts with oxygen to produce an electronically excited and highly reactive state of oxygen, known as singlet oxygen, which can interact with a large number of biological substrates as a result of its high chemical reactivity, inducing oxidative damage and ultimately lethal effects upon the bacterial cell by damaging the cell membrane and cell wall. Microorganisms that are killed by singlet oxygen include viruses, bacteria, protozoa and fungi. Singlet oxygen has a short lifetime in biological systems (<0.04μs) and a very short radius of action (0.02μm).

Due to its short lifetime, the migration of singlet oxygen from the site of its formation is limited, so initial cell damage is restricted to the localization of the photosensitizer. Thus, local application of the photosensitizer leads to a localized response and ensures the protection of distant molecules, cells and organs from side-effects

There are several factors influencing photodamage, including the type, dose, incubation time and localization of the photosensitizer, the availability of oxygen, the wavelength of light (nm), the light power density (mW/cm^2) and the light energy fluence (J/cm^2). An important characteristic of photodynamic therapy is its inherent dual selectivity; first by achieving an increased concentration of the photosensitizers by specific binding irradiation to a specified volume. In antibacterial photodynamic therapy, photodestruction is mainly caused by damage to the cytoplasmic membrane and DNA.

It seems that the primary cytotoxic agent responsible for the biological effects of the photo-oxidative process is singlet oxygen. Thus, the process of antimicrobial photodynamic therapy is generally mediated by a type II reaction, which is accepted as the major pathway in microbial cell damage.

Photosensitizer

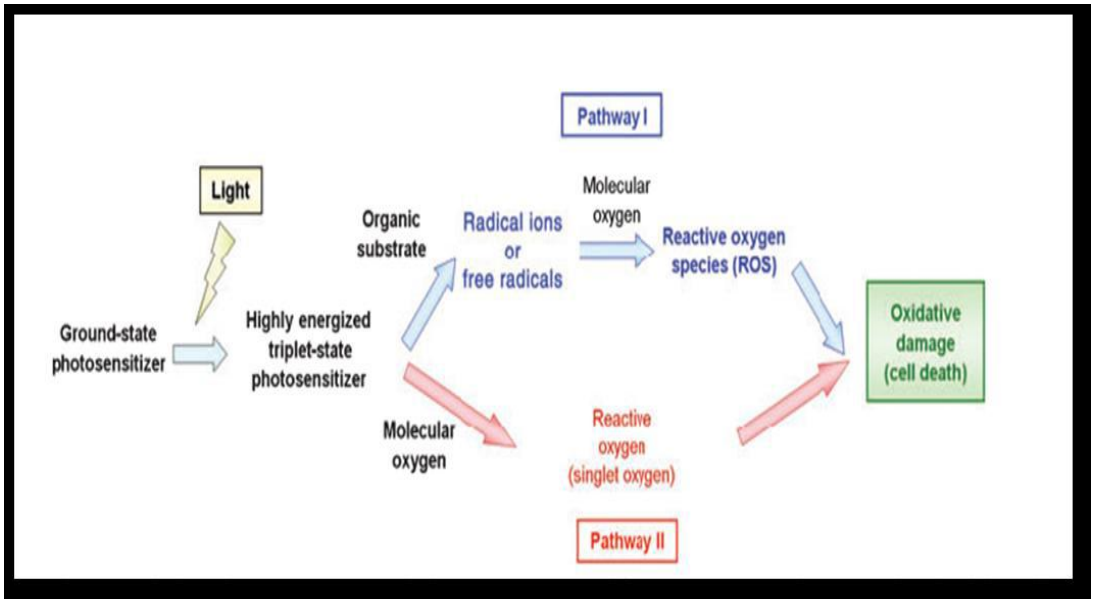
An important agent of aPDT is a photosensitizer, which should possess the following properties:

1. A high binding affinity for the given microorganism,
2. A broad spectrum of action,
3. A low binding affinity for mammalian cells to avoid the risk of photodestruction of host tissues
4. A low propensity for selecting resistant bacterial strains,
5. A minimal risk of promoting mutagenic processes, and low chemical toxicity

Gram positive bacteria are generally susceptible to photoinactivation, whereas gram-negative bacteria are often reported to be resistant to photodynamic action, unless the permeability of their outer membrane is modified.

Antimicrobial photosensitizers such as porphyrins, phthalocyanines and phenothiazines (eg- toluidine blue O and methylene blue), which bear a positive charge, can directly target both gram-negative and gram-positive bacteria. The positive charge seems to cause localized damage, which favours its penetration. Toluidine blue O and methylene blue are commonly used for oral antimicrobial photodynamic therapy. Toluidine blue O is a vital dye that has been used for staining mucosal abnormalities of the uterine cervix and oral cavity and for demarcating the extent of the lesions before excision. In addition it has been shown to be a potent photosensitizer for killing oral bacteria. Methylene blue has been used as a photosensitizing agent since the 1920s. It has been used to detect mucosal premalignant lesions and a marker dye in surgery.

Recently, the activation of photosensitizers has been achieved by diode lasers emitting light of a specific wavelength. These devices are portable and their cost is much lower compared with that of argon lasers, gallium-aluminum-arsenide diode lasers and helium-neon lasers, which have been mostly employed in photodynamic therapy.



Mechanism of photodynamic antimicrobial reactions at the molecular level

II. REVIEW OF LITERATURE

Fontana et al. 2009 aimed to assess the effectiveness of methylene blue-mediated photodynamic therapy both in the planktonic and the biofilm phase. Photodynamic therapy eliminated approximately 63% of bacteria in the planktonic phase, whereas only 32% of bacteria in biofilms, derived from the same plaque samples. In both cases a lower percentage of persistent bacteria was noted when the photosensitizer concentration was 50 µg rather than 25 µg.

Despite the lower effectiveness of photodynamic therapy in the reduction of biofilm bacteria as opposed to planktonic bacteria, the difference was only twofold, whereas antibiotics have been reported to be approximately 250-fold less effective under these conditions.

Phototherapy operates via killing bacteria, especially those having their own natural photosensitizer. It is particularly concerned with the oral black-pigmented perio-dontopathogens. Species such as Porphyromonas gingivalis, Prevotella intermedia, Prevotella nigrescens, and Prevotella melaninogenica account for the increased bleeding tendency of long-standing gingivitis and the development of periodontitis.

Prevotella spp. has also been recognized as potential producers of volatile sulfur compounds responsible for oral malodor (halitosis). The Soukos and Goodson studies have shown that broadband light ranging from 380 to 520 nm was able to achieve a threefold reduction in the growth of P. gingivalis and Prevotella species.

Dobson J and Wilson M .1992 conducted a study on biofilms of Streptococcus sanguis, Porphyromonas gingivalis, Fusobacterium nucleatum and Actinobacillus actinomycetemcomitans prepared on the surfaces of agar plates. Results showed Toluidine blue O and methylene blue enabled detectable killing of all four target organisms after exposure to light for 30 s. Aluminium disulphonated phthalocyanine, haematoporphyrin HCl and haematoporphyrin ester were effective photosensitizers of only some of the target organisms. These findings suggest that lethal photosensitization may be an effective means of eliminating periodontopathogenic bacteria from dental plaque.

Bhatti M et al. 2002 used red light in the presence of toluidine blue to kill Porphyromonas gingivalis and results showed that the fluidity of the organism's cytoplasmic membrane was found to decrease significantly during lethal photosensitization, and this was accompanied by membrane condensation and vacuolation of the cells. The disruption of membrane functions associated with decreased membrane fluidity may contribute to the bactericidal effect of light-activated toluidine blue.

O'Neill JF et al. 2002 irradiated multi-species biofilms of oral bacteria with light from a helium/neon laser in the presence of toluidine blue O (TBO). Results showed that Substantial numbers of oral bacteria in multi-species biofilms can be killed by light in the presence of TBO. This may be useful in the treatment of dental plaque-related diseases.

There have been numerous studies which showed beneficial effects with photodynamic therapy for treatment of periodontitis

Andersen et al. 2007 studied , effects of a single session of MB-mediated PDT (Periowave Treatment kit) and/or SRP on bleeding on probing, probing pocket depth and clinical attachment level Results showed that

SRP combined with PDT led to significant improvements of the investigated parameters over the use of SRP alone over a period of 3 months.

Christodoulides et al. 2008 studied effects of a single session of MB-mediated PDT (Helbo® Blue treatment kit) and ⁄ or SRP on full-mouth plaque score, full-mouth bleeding score, probing depth, gingival recession, clinical attachment and load of 11 periodontal pathogens PDT and SRP resulted in a significantly greater reduction in bleeding scores compared with scaling and root planing alone over a period of 6 months.

Lulic et al. 2009 reported the effects of repeated (five times within two weeks) MB-mediated PDT (Helbo® Blue treatment kit) and ⁄ or SRP on probing pocket depth, clinical attachment level and bleeding on probing. They concluded that repeated PDT as an adjunct to mechanical debridement led to significantly improved outcomes in all clinical parameters at 6 months.

Al-Zahrani & Austah 2011 did a study to evaluate photodynamic therapy (PDT) as an adjunctive treatment of chronic periodontitis with scaling and root planing (Sc/Rp) in smokers. Plaque index (PI), bleeding on probing (BOP), probing depth (PD), recession and clinical attachment level (CAL) were recorded. Diode laser of wavelength 670 nm was used. Results showed significant differences in favour of SRP + a PDT in CAL gain and PD reduction. But no significant differences in REC and BOP changes were found. They concluded that Photodynamic therapy might have an additional benefit to scaling and root planing when treating smokers affected with periodontitis.

Despite the beneficial effects of antimicrobial photodynamic therapy as clinically proven in previous studies , yet there are some studies which showed similar results with both photodynamic therapy and mechanical debridement for treatment of periodontitis.

Yilmaz et al. 2002 studied effects of a single session of MB-mediated PDT and ⁄ or mechanical subgingival debridement on the proportions of obligate anaerobes, plaque indices, bleeding on probing and probing pocket depth a randomized clinical study with a split-mouth design; 10 subjects with chronic periodontitis MB (50 μg ⁄ ml) was applied as a mouth rinse for 60 s followed by exposure of each papillary region to light at 685 nm from a 30 mW diode laser for 71 s. They found no additional microbiological and clinical benefits over conventional mechanical debridement over a period of 32 days.

Al-Zahrani et al. 2009 studied effects of a single session of MB-mediated PDT (Periowave ® Treatment kit) and ⁄ or SRP, and SRP + systemic doxycycline on plaque and bleeding scores, probing pocket depth, clinical attachment level and glycosylated hemoglobin level. A randomized clinical study; 45 subjects with type 2 diabetes and moderate to severe chronic periodontitis MB (50μg ⁄ ml) was applied in each site into periodontal pockets for 5–10 s followed by exposure to light at 670 nm for 60 s. Results showed no added benefit of PDT on clinical parameters or glycemic control was found over a period of 3 months.

Several studies have compared the effectiveness of treatment of residual pockets with photodynamic therapy, diode laser or deep scaling.

The use of photodynamic therapy, deep scaling and diode laser for the treatment of residual pockets in the trial of **Giannopoulou et al.2012** resulted in a significant clinical improvement for all three treatments and led to significant changes in several cytokines and acute phase proteins after treatment irrespective of treatment modality. It was indicated that aPDT and SRP suppressed Porphyromonas gingivalis, Tannerella forsythia and Treponema denticola more strongly, and resulted in fewer persisting pockets after 6 months than diode soft laser therapy.

Giannelli et al. 2012 compared the efficacy of photoablative and photodynamic diode lasers in adjunct to SRP and SRP alone for the treatment of chronic periodontitis. Initially, an 810 nm diode laser was used in photoablative (Pa) mode for removal of junctional, sulcular and outer gingival epithelium. Photoablative intra/extra-pocket de-epithelization with a diode laser was followed by single SRP and multiple photodynamic treatments (once weekly, 4-10 applications) using the 635 nm diode laser and 0.3% methylene blue as photosensitizer. The therapy effects were evaluated at the beginning and one year after treatment. The laser and SRP therapy enabled a significant reduction of PD (-1.9 mm) and BOP (33.2% bleeding sites) and gain CAL (1.7 mm) to be achieved. A reduction in the level of bacterial contamination, especially spirochetes, was also observed.

Pourabbas et al .2014 studied the effects of photodynamic therapy (PDT) as an adjunct to conventional scaling and root planing (SRP). He compared the clinical parameters and cytokine profiles in gingival Crevicular fluid of patients with moderate to severe chronic periodontitis. Single application of PDT using a 638-nm laser and toluidine blue. Results showed that only TNF-α was significantly improved in the PDT + SRP versus SRP group. Total levels of PMNs were reduced for all patients. They concluded that patients with CP, a single application of PDT did not provide any additional benefit to SRP in terms of clinical parameters or inflammatory markers 3 months following the intervention.

Studies on application of PDT for treatment of aggressive periodontitis

Deoliveira et al. 2007 reported on the outcome of antimicrobial photodynamic therapy monotherapy for the treatment of aggressive periodontitis. A total of 10 patients were randomly assigned to either photodynamic therapy (methylene blue + 60 mW diode laser) or scaling and root planing. Laser application was performed for 10 s per site after 3 mins of residence time of the photosensitizer. Three months later, both treatment procedures showed a reduction in pocket depth and gain in clinical attachment level, suggesting a potential clinical effect of photodynamic therapy as an alternative to scaling and root planing.

Novaes et al. 2012 investigated changes occurring in the subgingival microbiological composition of subjects with aggressive periodontitis treated with antimicrobial photodynamic therapy in a single episode or SRP. This trial indicated that aPDT is more efficient in reducing the presence of Aggregatibacter actinomycetemcomitans than SRP. On the other hand, SRP limited the number of periodontal pathogens of the Red Complex more effectively than aPDT.The authors concluded that both methods (SRP and aPDT) should be combined to gain better results in non-surgical treatment of aggressive periodontitis.

Arweiler et al. 2013 compared the short-term effects of nonsurgical periodontal therapy with the additional administration of systemic antibiotics (AB) and the same therapy with additional photodynamic therapy (PDT) in the treatment of patients with aggressive periodontitis (AP). Thirty-six patients divided into two groups of 18 subjects each with AP received full-mouth nonsurgical periodontal treatment (SRP). Group AB received amoxicillin and metronidazole three times a day for 7 days. Group PDT received two applications of PDT on the day of SRP as well as at follow-up after 7 days. Statistically significant clinical improvements were seen after 3months. However systemic administration of antibiotics resulted in significantly higher reduction of PD and a lower number of deep pockets compared to PDT.

Effect of antimicrobial photodynamic therapy on bone levels

Photodynamic therapy and its effect on bone.

Komerik et al. 2003 demonstrated, in a histological examination using rats, that, 90 days post treatment, toluidine blue O-mediated photodynamic therapy had induced a decrease in alveolar bone loss around teeth with experimentally induced periodontitis.

De Almeida et al. 2007 compared, histologically and radiographically, the progression of experimentally induced periodontitis after treatment with methylene blue alone, low-level laser therapy alone, or with methylene blue followed by low-level laser therapy (photodynamic therapy). The results of radiographic evaluation demonstrated that photodynamic therapy had a short-term effect (up to 15 days) upon the reduction of periodontal tissue destruction. However, at 30 days there were no significant differences between the groups.

Brink and Romanos 2007 compared the clinical and microbiological effects of scaling and root planing with Nd:YAG laser (2W), scaling and root planing with 980 nm diode laser (2W), and scaling and root planing with antimicrobial photodynamic therapy [methylene blue + 670 nm diode laser (75 mW)] and scaling and root planing alone in patients with chronic periodontitis. They reported that in the group treated with antimicrobial photodynamic therapy + scaling and root planing, bleeding on probing was reduced significantly more, one to three months following treatment, than in the other groups. In addition, the bactericidal effects of scaling and root planing with antimicrobial photodynamic therapy appeared to be greater than those of the scaling and root planing with Nd:YAG laser, scaling and root planing with diode laser, or scaling and root planing alone treatments.

SUMMARY

Antimicrobial photodynamic therapy seems to be an attractive option as a non-invasive and low-cost treatment approach in the field of Periodontology

Because antimicrobial photodynamic therapy can be administered locally, a high concentration of the chemical agent can be achieved at the locus of infection, enabling efficient bacterial elimination without inducing bacterial resistance.

Although many studies assessing the effectiveness of antimicrobial photodynamic therapy have not so far indicated superiority of aPDT compared to conventional periodontitis treatment, aPDT adjunctive to SRP improves clinical and microbiological parameters.

Furthermore, using aPDT can achieve the same clinical outcomes compared to nonsurgical treatment, whereas antimicrobial photodynamic therapy is a non-invasive modality that allows the prevention of damage to hard and soft periodontal tissues.

The use of low-level energy lasers in aPDT can exert an additional positive influence on the healing of periodontal tissues as a result of the potential biomodulatory effects, such as the stimulation and proliferation of cells.

Antimicrobial photodynamic treatment has been reported to be effective as an adjunct to conventional therapy to destroy bacteria in sites where there is limited access for mechanical instrumentation as a result of the anatomical complexity of the roots

Biofilm resistance to antimicrobial photodynamic therapy still remains the challenge for medical researchers. Development of novel delivery and targeting approaches may help to overcome the low biofilm susceptibility to aPDT and allow aPDT to become a new, efficient modality of periodontitis treatment.