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Review Article

An Insight in to Photodynamic Therapy

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Abstract

Periodontitis is the chronic inflammation of supporting structures of teeth and is the major reason for tooth loss. The objective of periodontal therapy is to reduce the bacterial burden. Non-surgical therapy is considered as the gold standard technique of periodontal therapy. Phototherapy using low level lasers is called photodynamic therapy. Photodynamic therapy targets the specific pathogen without damaging the host tissue. This is effective for killing drug resistant pathogens and in treating multidrug resistant infection. Photodynamic therapy has three different components i.e. light, photosensitizer and oxygen. There are two mechanisms in antimicrobial photodynamic therapy. One is DNA damage and the second method is damage to the bacterial cytoplasmic membrane resulting in inactivation of the membrane transport system, inhibition of plasma membrane enzyme activities, lipid peroxidation and others. In photodynamic therapy bacterial killing is mainly by damaging the cytoplasmic membrane of bacteria. It has different applications in various fields of dentistry. In periodontics it is used for treating both periodontitis and periimplantitis. The adjunctive use of PDT to scaling and root planning in the treatment of patients with chronic periodontitis, aggressive periodontitis and periimplantitis, resulted in greater clinical attachment level gains, reduction in bleeding on probing and probing pocket depths. The aim of this review is to describe briefly about the photodynamic therapy and its uses and evidences in periodontics and implant dentistry.

Keywords: Periodontitis; Anti-Microbial Photodynamic Therapy; Photosensitizer Dye; Management of Periimplantitis; Laser Light

Introduction

Periodontitis is the inflammation of the supporting structures of the teeth caused by various pathogenic microorganisms [1]. The main objective of periodontal therapy is the elimination of bacteria and bacterial niches by removing the supragingival and subgingival plaque [2]. Plaque removal is done by means of mechanical debridement, which is a non-surgical therapy. Mechanical debridement alone cannot remove all the periodontal pathogens especially in areas of the complex root anatomy like furcation's and concavities in deeper pockets and those bacteria residing in the soft tissues [3]. Potential periodontal pathogens like Aggregatibacter actinomycetemcomitans and Prohormones gingival is invade deeper periodontal tissues and disrupt host epithelial cells hence they are not completely removed by mechanical debridement [4,5].

Antimicrobial therapy or antiseptics when applied directly in to the periodontal pockets reduce the periodontal pathogens. Systemic antibiotics are also used to reduce the periodontal pathogens. So along with mechanical debridement local or systemic chemotherapeutics are used for treatment of periodontitis [6,7]. But there are two major drawbacks associated with antimicrobial therapy that are difficult to maintain a stable concentration for a long period of time [8] and the drug resistance by pathogens [9].

Phototherapy has been introduced as new treatment approach in periodontics in the beginning of 1990's. Lasers are used for decontaminating periodontal pockets [10,11]. High level laser possess bactericidal properties by direct ablation or thermal denaturation or destruction of bacterial cells [11,12]. But there are limited clinical evidence to show that laser causes greater reduction in sub gingival bacteria compared with conventional mechanical therapy [13]. More over high level lasers causes irreversible thermal damage of surrounding periodontal tissues and excessive ablation or thermal coagulation, carbonization or necrosis of the root, the gingival connective tissue, the bone and the pulp tissues [11,14,15].

The noninvasive phototherapy using low level lasers is called photodynamic therapy. Photodynamic therapy targets the specific pathogen without damaging the host tissue [16,17]. Other names of photodynamic therapy(PDT) are photodynamic inactivation (PDI) [18] lethal photosensitization, photoactivated disinfection (PAD) or photodynamic antimicrobial chemotherapy (PACT) [19], photodynamic disinfection or lethal photosensitization. This is effective for killing drug resistant pathogens and in treating multidrug re-

sistant infection. It is an alternative to antibacterial, antifungal, and antiviral treatment for drug-resistant organisms.

In the oral cavity periodontal diseases are effectively treated with photodynamic therapy. Photosensitization can kill the multi-resistant Gram-negative hospital strains [20]. Apart from killing of microorganisms PDT destroys the important virulence factors of Gram-negative bacteria e.g. endotoxins and proteases [21-23].

History

Phototherapy had its origin in ancient Greece, Egypt and India. In the beginning of the 20th century it was rediscovered by the Western civilization. Danish physician, Niels Finsen in 1901 first reported the contemporary photodynamic therapy. He used photodynamic therapy for the treatment of Lupus Vulgaris by using heat filtered light from a carbon arc lamp (The Finsen Lamp). He won a Nobel prize for phototherapy in 1903. Medical student of Professor Herman Von Tappeiner in Munich, Osar Raa reported that the cell death in photodynamic therapy occurs by the interaction of chemicals and lights. When he was studying the effects of acridine on paramecia cultures, he accidently discovered that when light falls on acridine red it lethally affect infusoria, which is a paramecium species. Von Tappeiner stated that oxygen was essential for photodynamic therapy and in 1907 he coined the term "Photodynamic action".

Thomas Dougherty and co-workers [24] of Roswell Park cancer institute, Buffalo, New York in 1978 conducted the first clinical trial. They treated 113 cutaneous or subcutaneous malignant tumors by photodynamic therapy using hematoporphyrin derivative as the photosensitizer, they concluded that there was a total or partial resolution of 111 tumors. John Toth again named this as Photodynamic therapy. In 1999 Food and Drug Administration approved photodynamic therapy for treatment of pre-cancerous skin lesions of the face or scalp. Then photodynamic therapy emerged as a new non - invasive therapeutic option.

Components of Photodynamic Therapy

Photodynamic therapy has three basic components. They are visible light, nontoxic photosensitizer and oxygen. The principle is that when photosensitizer (i.e. a photoactivatable substance) binds to the target cells and is activated by light of a suitable wavelength singlet oxygen and other reactive oxygen species are produced which are toxic to certain cells and bacteria (Figure 1).

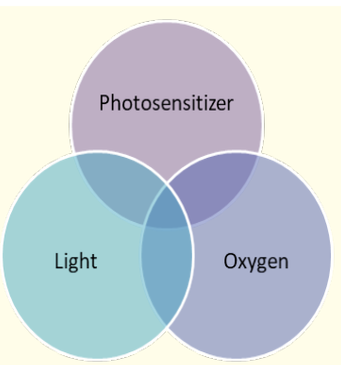

Figure 1: Components of photodynamic therapy.

Light

Photosensitizer was activated in the past by a variety of light sources such as argon lasers, potassium titanyl phosphate or neodymium doped: yttrium, aluminum and garnet (Nd: YAG) lasers. Now the light sources are those of helium - neon lasers (633 nm), gallium-aluminum-arsenide diode lasers (630 - 690, 830 or 906 nm) and argon lasers (488 - 514 nm). The wavelengths of these lasers range from visible light to the blue of argon lasers or from the red of helium - neon and gallium - aluminum - arsenide lasers to the infrared area of some diode lasers. High energy laser irradiation is not used to activate the photoactive dye since relatively low-level exposure produces high bactericidal effect. Non-laser light sources like light-emitting diodes (LED) are now used for activating photosensitizers in photodynamic therapy because LED devices are more compact and portable and are cheap when compared with that of traditional lasers [25-27].

Photosensitizer

Photosensitizers are the dye which get absorbed by the microorganism, cells or tissue and they interacted with light of suitable wavelength when get exposed. The photosensitizer is applied in the targeted area either by topical application or aerosol delivery or interstitial injection. For activating the photosensitizer the light must be of a specific wavelength. The following are the desirable properties of the photosensitizer:

- High binding affinity for the given microorganism,
- Broad spectrum of action,
- Low binding affinity for mammalian cells to avoid the risk of photo destruction of host tissues,
- Low propensity for selecting resistant bacterial strains,
- Minimal risk of promoting mutagenic processes,
- Low chemical toxicity,
- Have an excellent photochemical reactivity,
- Only be toxic in the presence of light,
- preferable retention by target tissue,
- Rapidly excreted from the body,
- Non -toxic and activated upon illumination.

Various Photosensitizers are:

- Tricyclic dyes with different meso Acridine orange, proflavine, riboflavin, methylene blue, fluorescein and erythrosine.
- Tetrapyrroles. e.g.: Porphyrins and derivatives, chlorophyll, phylloerythrin and phthalocyanines.
- Furocoumarins. e.g.: Psoralen and its methoxy derivatives, xanthotoxin and bergapten.

In antimicrobial photodynamic therapy the commonly used photosensitizers are toluidine blue O, methylene blue, erythrosine, chlorine e6 and hematoporphyrin. The phenothiazine dyes (toluidine blue O and methylene blue) are the major photosensitizers

used in the medical field. They have similar characteristic features and are used for the inactivation of both gram-positive and gram-negative periodontopathic bacteria [28-30]. They bind to the outer membrane of gram-negative bacteria and penetrate bacterial cells [31-33] or selectively kills the microorganisms without damaging the host mammalian cells [34]. Toluidine blue O and methylene blue are selected as the photosensitizers of choice in the treatment of periodontitis and peri-implantitis. Among this toluidine blue O has a greater ability for killing gram-positive and gram-negative bacteria compared with methylene blue. Studies shows that *A. actinomycetemcomitans, P. gingival* is and *Fusobacterium nucleatum* are more effectively eliminated with toluidine blue O compared with methylene blue [35]. *In vitro* study showed that toluidine blue O interacts with lipopolysaccharide more effectively than methylene blue [36] therefore toluidine blue O has greater photo bactericidal effect of against gram-negative bacteria compared with methylene blue [37].

Mechanism of Action

There are two mechanisms involved in antimicrobial photodynamic therapy. One is DNA damage and the second method is damage to the cytoplasmic membrane of bacteria [38] resulting in inactivation of the membrane transport system, inhibition of plasma membrane enzyme activities, lipid peroxidation and others [39]. In photodynamic therapy bacterial killing is mainly by damaging the cytoplasmic membrane of bacteria [40].

When a photosensitizer is irradiated with light of specific wavelength it undergoes a transition from a low-energy ground state to an excited singlet state. Then the photosensitizer may either decay back to its ground state, with emission of fluorescence, or may undergo a transition to a higher-energy triplet state. The triplet state can react with endogenous oxygen to produce singlet oxygen and other radical species resulting in rapid and selective destruction of the target tissue. The utilization of oxygen in the production of reactive oxygen species is known as photochemical oxygen consumption.

The longer lifetime of the triplet state helps in the interaction of the excited photosensitizer with the surrounding molecules, and cytotoxic species [41]. The triplet-state photosensitizer enters in to two different pathways (type I and II) to react with biomolecules [41,42].

In Type I reactions hydrogen-atom abstraction or electron-transfer reactions occurs between the excited state of the photosensitizer and the organic substrate molecule of the cells resulting in production of free radicals and radical ions. These free-radical species are 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 resulting in irreparable biological damage [43,44].

In the type II reaction, the triplet-state photosensitizer reacts with oxygen to produce an electronically excited and highly reactive state of oxygen, known as singlet oxygen ($^1O_2$), which interact with a large number of biological substrates as a result of its high chemical reactivity induces oxidative damage and ultimately produce lethal effects on the bacterial cell by damaging the cell membrane and cell wall [43,44].

Microorganisms including viruses, bacteria, protozoa and fungi are killed by singlet oxygen. Singlet oxygen has a short lifetime in biological systems (< 0.04 ls) and a very short radius of action (0.02 lm) [45]. Because of the short life time singlet oxygen have short migration from its site of formation and the sites of initial cell damage by photodynamic therapy are closely related to the localization of the photosensitizer. Thus, the reaction takes place within a limited space resulting in a localized response and make it ideal for application at localized sites without affecting distant molecules, cells or organs.

The primary cytotoxic agent responsible for the biological effects of the photo-oxidative process is singlet oxygen. 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 [46].

Application of Photodynamic Therapy in Dentistry

Application of photodynamic therapy led to significant advances in dentistry because the delivery of light is more accessible and topical application of the photosensitizer is more feasible in the oral cavity. Photodynamic therapy is used in the treatment of different types of oral solid tumors, and investigations are done for the application of photodynamic therapy to treat superficial precancerous oral lesions, such as oral leukoplakia, oral erythroleukoplakia and oral verrucous hyperplasia [47,48]. Photodynamic therapy has been effectively applied in the treatment of lichen planus [49,50]. The antimicrobial properties of photodynamic therapy make it suitable for the treatment of bacterial, fungal and viral infections of the oral cavity.

In operative dentistry the antimicrobial photodynamic therapy technique is effective for the treatment and prevention of dental caries. This is effective against gram-positive bacteria such as *Streptococcus subrings, Streptococcus mutants* and *Streptococcus sanguinis*, which are important in the etiology of dental caries [51-53].

In endodontics, antimicrobial photodynamic therapy is used as an effective adjunct to conventional endodontic disinfection treatment to destroy the bacteria that remain even after irrigation with sodium hypochlorite [54]. Several studies showed that this was effective in eliminating anaerobic and aerobic bacteria, including Enterococcus faecalis, and Actinomyces, Porphyromonas and Prevotella spp in primary endodontic lesions as well as in cases of endodontic treatment failure [55-57].

Several studies demonstrated that antimicrobial photodynamic therapy is highly effective in the destruction of Candida albicans, which is responsible for oropharyngeal candidiasis [58-60]. Antimicrobial photodynamic therapy has also been reported to be successful in treating viral infections, including common labial herpes simplex infection, as it has been demonstrated ultra structurally that the viral envelope which protected the virus from adsorption or penetration is photodamaged by antimicrobial photodynamic therapy [61,62].

Antimicrobial Photodynamic Therapy in Periodontics

Antimicrobial photodynamic therapy resolve the difficulties and problems of conventional antimicrobial therapy and used as an adjunctive to conventional mechanical treatments. The photosensitizer is placed directly in the periodontal and peri-implant pocket and the liquid agent can easily access the whole root or implant surface and are activated by the laser light through placement of the optical fiber directly in the pocket. Due to technical simplicity and the high effectiveness of bacterial killing, the antimicrobial photodynamic therapy is used in the treatment of periodontal and peri-implant diseases.

Periodontopathogen microbes like *Prevotella intermedia, Porphyromonas gingival* is, *Fusobacterium nucleatum* and *Actinobacillus actinomycetemcomitans* are significantly decreased by photodynamic therapy [63].

In peri-implantitis the causative bacteria are similar to the pathogens for the periodontal diseases [64,65] so disinfection and detoxification of the diseased implant surface, as well as the peri implant pockets are essential for effective healing with regeneration of the lost bone around the affected implants. Conventional mechanical methods are ineffective for complete debridement of the bone defect as well as the contaminated microstructure implant surface [66-68]. Adjunctive application of systemic or local antibiotics and antiseptics has been generally recommended [69-71]. However because of the potential problems related to antibiotics (such as resistance) and antiseptics [72] and the generally insufficient effect of the antimicrobial agents for bacterial eradication as well as poor results of re-osseointegration following their adjunctive application during nonsurgical and surgical therapy of peri-implantitis, novel approaches are still necessary in the treatment of peri-implant diseases.

The adjunctive use of PDT to scaling and root planning in the treatment of patients with chronic periodontitis, aggressive periodontitis and periimplantitis, resulted in greater clinical attachment level gains, reduction in bleeding on probing and probing pocket depths. Azarpazhooh., *et al.* [73] conducted a systematic review and concluded that photodynamic therapy as an independent therapy or as an adjunct to SRP was not superior to control treatment. A meta-analysis was performed by Sgolastra., *et al.* [74] suggested that the use of aPDT as an adjunct to conventional treatment provides short-term benefits in terms of CAL gain and pocket depth reduction (at 3 months after treatment) thereby confirming the safety of PDT.

Novae's., *et al.* 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. Because of the fact that aPDT and SRP affect different species, it is suggested that both methods combined to gain better results in non-surgical treatment of aggressive periodontitis [75].

Antibody targeted antibacterial approach using photodynamic therapy

Antibodies conjugated with photosensitizers are used to target *Staphylococcus aureus* [76]. Selective killing of *P. gingivalis* achieved in presence of *Streptococcus sanguinis* or in human gingival fibroblasts using a murine monoclonal antibody against *P. gingivalis* lipopolysaccharide conjugated with toluidine blue O. Bacteriophages were used as vehicles to deliver the photosensitizer. The combination of pulsed laser energy and absorbing gold nanoparticles conjugated with antibodies selectively kills the microorganisms. The energy absorbed by nanoparticles during irradiation was quickly transferred in to heat through nonradioactive relaxation resulting in bubble formation around clustered nanoparticles leading to irreparable bacterial damage.

Nanoparticle based antimicrobial photodynamic therapy

In order to avoid incomplete penetration of photosensitizer, a new delivery system is introduced for improving pharmacological characteristics. A newer technique of encapsulation of methylene blue within poly (D,L-lactide- co-glycolide) (PLGA) nanoparticles (150 - 200 nm in diameter), enhances drug delivery and photo destruction of oral biofilms [77].The nanoparticle matrix PLGA is a polyester co-polymer of polylactide and polyglycolide that has received approval by the US Food and Drug Administration because of its biocompatibility and its degradation in the body through natural pathways [78]. Nanoparticles were not internalized by microorganisms, but they were mainly concentrated onto their cell walls. Thus the cell wall become permeable to methylene blue released by the nanoparticles. Nano agent has several favorable properties for use as a photosensitizer [79]:

- A large critical mass (concentrated package of photosensitizer) for the production of reactive oxygen species that destroy cells;
- It limits the cells ability to pump the drug molecule back out and reduces the possibility of multiple drug resistance;
- Selectivity of treatment by localized delivery agents, which can be achieved by either passive targeting or by active targeting via the charged surface of the nanoparticle;
- The nanoparticle matrix is non-immunogenic.

Advantages of Photodynamic Therapy

- Non-invasive local therapy
- Thorough irrigation and elimination of pathogens in inaccessible areas of periodontal pocket within short span of time, thus beneficial to both operator and the patient
- The risk of bacteremia after periodontal debridement can be minimized. Useful in patients with at-risk medical history
- There is no need to prescribe antibiotics, therefore the possibility of side effects is avoided.
- There is no need to anaesthetize the area and destruction of bacteria is achieved in a very short period (<60 seconds).
- Development of resistance to the PDT is less
- Non-surgical protocol required for the application of the photosensitizer
- No damage to the adjacent host tissues [80,81].

Risk and Side Effects of Photodynamic Therapy

The side effects of photodynamic therapy falls under two categories i.e. effects due to light energy and effects of photosensitizer and photochemical reaction. The effects of light energy are inadvertent irradiation to the eye and thermogenesis. Both this can be managed by usage of protective eye wear and usage of low level diode laser. The toxicity of the photosensitizer to periodontal tissues because of the fact that the photosensitizer alone can exhibit bactericidal action [82]. Most of the dyes used in aPDT adhere strongly to the soft tissue surface of the periodontium, causing retention of the dyes in the pocket. Their presence, even for a short time, can negatively affect periodontal tissue attachment healing. The dye solution is not routinely removed clinically after a completed aPDT application, which causes temporary pigmentation of the periodontal tissue. It is unfavorable for the patient's aesthetics. Thus, the use of photosensitizers with a paste base instead of liquids has been suggested, because pastes can be easily removed after the treatment [83].

Applications of Photodynamic Therapy

- PDT can be used in Non-surgical treatment of aggressive periodontitis.
- Treating periodontal pockets.
- Plaque-infected cervical regions of teeth and implants.
- Disinfecting oral tissues prior to and during surgery.
- Treating oral candidiasis in immunocompromised patients.
- Guided bone regeneration.
- Photo dynamic therapy in implantology: Laser PDT can be used in implantology to promote osseointegration and to prevent peri implantitis.

Future Perspectives

Periodontal debridement is less effective in removing the biofilm in the periodontal pockets. Photodynamic therapy is an adjunctive method for improving the clinical aspect of periodontal tissues and also helps in reducing of bleeding on probing. This is technically simple and effective method in bacterial eradication. The concept of photodynamic therapy is that it selects the target tissue by marking it with the photosensitizer, and then light of suitable energy is focused on marked cells or tissues. The use of low-level energy lasers (i.e. diode lasers) is reported to exert additional positive effects on the surrounding tissues and cells i.e. they helps in the healing of periodontal tissues as a result of the potential biomodulator effects, such as stimulation and proliferation of cells. Another important aspect of antimicrobial PDT is its ability to destroy secreted virulence factors. The clinical applications of antimicrobial PDT have been slow but steady. Though limited clinical trials have been conducted for different diseases using PDT its intensive use in periodontitis has given hope that it can be used clinically to treat a number of other infectious diseases. Development of new photosensitizers, more efficient light delivery systems and further studies are required to establish the optimum treatment parameters.

Conclusion

There are many studies assessing the effectiveness of antimicrobial photodynamic therapy but the superiority of aPDT compared to conventional periodontitis treatment is not confirmed. Moreover aPDT is used as an adjunctive to SRP to improves clinical and microbiological parameters. aPDT have same clinical outcomes compared to nonsurgical treatment, but advantage of antimicrobial photodynamic therapy is that it is a non-invasive treatment modality and it prevents the damage to hard and soft periodontal tissues. The low-level energy lasers in aPDT provides an additional positive influence on the healing of periodontal tissues because of the potential biomodulatory effects, such as the stimulation and proliferation of cells. However nonsurgical treatment is still the gold standard of chronic periodontitis treatment. aPDT may be used as an alternative therapeutic strategy for residual pocket treatment in supportive periodontal maintenance. 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 because of the anatomical complexity of the roots.

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