



## ANTIMICROBIAL PHOTODYNAMIC THERAPY

### Dental Science

<b>Dr. Nupur Sah-</b>	Reader and Guide, Department of Periodontics, Y.M.T Dental College and Hospital, Kharghar, Navi Mumbai-410210
<b>Dr. Kavita Pol Nalawade</b>	Reader and Guide, Department of Periodontics, Y.M.T Dental College and Hospital, Kharghar, Navi Mumbai-410210.
<b>Dr. Jyotsna Anjankar</b>	PG student 3rd year, Department of Periodontics, Y.M.T Dental College and Hospital, Kharghar, Navi Mumbai-410210
<b>Dr. Sneha K. Rohra</b>	PG student 1st year, Department of Periodontics, Y.M.T Dental College and Hospital, Kharghar, Navi Mumbai-410210.

### ABSTRACT

Periodontitis is a multifactorial disease that is associated with loss of the supporting tissues around the tooth. A major objective of periodontal therapy is to remove soft and hard, supragingival and subgingival deposits from the root surface to stop disease progression. Although non-surgical periodontal treatment may result in significant clinical improvements, none of the currently available instrumentation techniques are effective in completely eliminating subgingival bacteria and calculus. Photodynamic therapy is a new type of non-invasive phototherapy for bacterial elimination, which uses low-level laser light and selectively targets the bacteria without potentially damaging the host tissues.

### KEYWORDS:

photodynamic therapy, bacteria, periodontal disease

### INTRODUCTION

Non biostimulative effect of Low level laser therapy (LLL) 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. Photodynamic therapy is also known as photoradiation therapy, phototherapy or photochemotherapy.<sup>1</sup> The use of photodynamic therapy for inactivating microorganisms was first demonstrated more than 100 years ago, when Oscar Raab<sup>2</sup> 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 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 - The photosensitizer is a compound that is capable of absorbing light of a specific wavelength and transforming it into useful energy. Eg., Methylene blue, Toluidine blue.

3. Oxygen - The photosensitizer 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.

Each factor is harmless by itself, but when combined they can produce lethal cytotoxic agents that can selectively destroy cells.<sup>3</sup>

### PHOTOSENSITIZER

An important agent of Antimicrobial Photodynamic Therapy (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.<sup>7</sup> 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.<sup>8</sup> 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.<sup>9</sup> It has been used to detect mucosal premalignant lesions and a marker dye in surgery. Recently a new photosensitizer called Indocyanine green (ICG), a tri-carbocyanine that belongs to family of cyanine dyes has

been developed. It is widely used in the fields of Ophthalmology and Cardiac imaging. Recent in vitro studies have reported its efficacy in killing potent periodontal pathogens like *A. actinomycetemcomitans* and *P. gingivalis* when combined with 810 nm diode laser. Indocyanine green has proven effectiveness as a light-activated antibacterial agent, for adjunctive use in wound healing or treating chronic infections of mucous membrane and skin.

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.

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 photosensitizers in triplet state react with biomolecules via two mechanisms:

#### Type 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.<sup>4,5</sup>

#### 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.<sup>4,5</sup> Microorganisms that are killed by singlet oxygen include viruses, bacteria, protozoa and fungi. Singlet oxygen has a short lifetime in biological systems (<0.04 $\mu$ s) and a very short radius of action (0.02 $\mu$ m).<sup>6</sup> 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. 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.

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<sup>2</sup>) and the light energy fluence (J/cm<sup>2</sup>).

#### USES OF ANTI-MICROBIAL PHOTODYNAMIC THERAPY IN PERIODONTICS

- As an alternative to chemical antimicrobial agents to eliminate subgingival species and treat periodontitis.
- Management of peri-implantitis.

#### 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.

Betsy et al. 2014<sup>12</sup> conducted a study to evaluate the potential of antimicrobial photodynamic therapy (aPDT) as an adjunct to scaling and root planing (SRP) in the treatment of chronic periodontitis. Statistically significant improvements in terms of clinical parameters were seen at the end of 3 months and 6 months, in terms of halitosis significant difference was recorded at the end of 1 month, which did not persist long. They reported that aPDT acts as a beneficial adjunct to SRP in non-surgical treatment and management of chronic periodontitis in short-term.

Srikanth K et al (2015)<sup>13</sup> evaluated the effects of indocyanine green (ICG) as an adjunct to nonsurgical periodontal therapy in terms of reduction in percentage of viable bacteria and host tissue injury. They concluded that laser activated ICG dye may enhance the potential benefits of SRP and can be used as an adjunct to nonsurgical periodontal therapy.

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.

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