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Role of Antimicrobial Photodynamic Therapy in Oral White Lesions: An Overview

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Abstract:-
There are diverse oral white lesions which present a diagnostic and therapeutic challenge to the modern day dental clinicians. There are various treatment modalities like LASER ablation,cryotherapy,surgical excision etc. But non-surgical therapy possess risk of recurrence and surgical excision can cause scar tissue formation. APDT is an alternative treatment option which uses synergistic interaction between photosensitizers and light of specific wavelength to induce target tissue destruction and modulate local immune response. This review provides mechanism of action and application of APDT. It can be a valuable tool for oral health care professionals for treating oral white lesions and can lead towards a more effective and minimally invasive treatment option.

Key words:-
Antimicrobial Photodynamic therapy, oral white lesions, Photosensitizers, light source, Aminolevulinic Acid, Methylene Blue, Toludine Blue,Oral Leukoplakia

I. INTRODUCTION :

The term "oral white lesions" refers to a broad spectrum of disorders that are characterized by abnormal white patches or plaques on the oral mucosa. These lesions require appropriate clinical attention and effective diagnosis because they represent a wide range of diseases, from persistent irritations to potentially malignant conditions. Numerous etiologies include autoimmune reactions, microbial infections, persistent inflammation, and harmful practices like tobacco addiction etc[1].Oral white lesions can appear white for a variety of reasons, including Hyperkeratosis (elevated keratin production), Acanthosis (abnormal thickening of stratum spinosum), Edema (fluid buildup within and outside of cells), Pseudo-membrane development (caused by the necrotic epithelium caused by harmful substances, fungus, etc.)[1]

These lesions provide crucial visual clues for diagnosis; nevertheless, to ascertain their exact nature and ascertain the underlying cause and potential for malignancy, a clinical examination, biopsy, and histopathological evaluation are frequently necessary[3].

For the treatment of oral white lesions (such as leukoplakia, oral verrucous hyperplasia, and oral lichen planus), several therapeutic modalities have been put forth.Topical treatments such as vitamin A, antibiotics, and steroids are among the available therapy options. Oral white lesions can be removed via cryosurgery, laser ablation, electro-cauterization, or surgical excision.Although non-surgical methods of treating oral white lesions have a high recurrence rate, they could be helpful in the short term.Moreover, it has been shown that treating oral white lesions surgically results in higher morbidity and the formation of scar tissue[2].

Over the past few decades, antimicrobial photodynamic therapy (APDT) has become a well recognized minimally invasive therapeutic option on a global scale. The definition of Antimicrobial Photodynamic treatment (APDT) is a technique that produces reactive oxygen species (ROS) in an oxygen-containing environment by using light energy and a photosensitizer (PS)[9]. Oral white lesions respond well to APDT treatment because of its low morbidity rate, good functional and esthetic results, and minimum scarring[2]. Jodlbaner and Von Tappeiner first used the term "photodynamic" in 1904 to refer chemical processes that need oxygen and are triggered by photo-sensitization[6]. APDT was authorized by the US Food and Drug Administration in 1999 to treat precancerous skin lesions on the face[6].

There is ample evidence supporting the use of aPDT for a variety of illnesses and ailments, including diabetic foot, chronic skin ulcers, and infected leg ulcers [10]. Its activity specifically targets the oral environment, treating conditions

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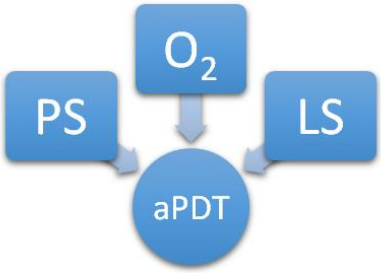
including peri-implantitis, lichen planus, leukoplakia, periodontal pockets etc [10].

There is a lesser risk of compromising the integrity of underlying tissue architecture with aPDT than with laser ablation techniques and other invasive methods as it is a cold photochemical process that does not involve tissue heating and leaves connective tissues, such as collagen, mostly intact at the treatment site[9].

CONCEPTS OF APDT:

For the treatment of oral white lesions, APDT is a relatively new adjuvant therapy.APDT is made up of three basic components: oxygen, a photosensitizer, and a specific visible light wavelength. The PS is administered mostly either topically or intravenously . The light activates the photosensitizer, which sets off a chain of photochemical processes that eventually cause the death or damage to the aberrantly proliferative cells[3] .When a certain wavelength of visible light induces biochemical reactions in the presence of PS, PS changes into an excited state and releases reactive oxygen species such singlet oxygen and free radicals, which specifically destroy cells, lyse membranes, and inactivate proteins[3].Its effectiveness varies according to various case reports and articles, ranging from total lesion regression to a partial response to no reaction at all.



OXYGEN:

APDT cannot cause its harmful effects on the target cells in the absence of oxygen. The light stimulates the photosensitizer molecule from its stable ground state to an unstable singlet state and a relatively long-lived triplet state when it absorbs a photon within a lesion. Reactive oxygen species (ROS) are created when the activated molecule transfers energy to oxygen in order to return to the stable ground state[4]. ROS are very cytotoxic, have a brief half-life, a narrow range of action, and they destroy dysplastic cells, which results in tissue necrosis and swelling[4]. At last, this tissue is destroyed, and the treated area experiences normal healing and re-epithelialization.

PHOTOSENSITIZERS :

Photosensitizers are certain chemical substances that may be activated by absorbing a particular light wavelength from a light source. These chemical compounds absorb light energy and use it to fuel a chemical reaction with molecular oxygen to create reactive oxygen species including superoxide and singlet oxygen, which are damaging to cells both directly and indirectly[5].

PSs may be divided into three major families based on their chemical compositions and places of origin:

1) .Porphyrin-based (e.g. Photofrin, 5-aminolevulinic acid)

2) Chlorophyll-based (e.g. Purpurins, Bacteriochlorins etc)

3) Dyes (e.g. Phtalocyanine, Napthalocyanine etc)[4].

The porphyrin family comprises the majority of the clinical PSs that are currently available[4].

5-aminolevulinic acid (5-ALA), A second-generation photosensitizer, , has the following properties such as a relatively low molecular weight; a shorter phototoxicity period (24–48 hours), strong tissue penetration; and a high rate of production of singlet oxygen[4].Although the use of alternative same generation photosensitizers, such as hypericin and phthalocyanine, has also been documented, it is the most commonly utilized photosensitizer for the treatment of oral white lesion by aPDT[4]. 5-ALA is water soluble and can be administered orally or intravenously. Since ALA is only a precursor to porphyrin, it is unable to create ROS on its own. Through the porphyrin–haem route, exogenous ALA penetrates cells and is endogenously transformed into porphyrin IX (PpIX)[3]. Reactive oxygen species are produced after PpIX is exposed to visible light, especially its absorption peak at 400–410 nm and 635–645 nm[4]. Moreover, ALA has strong tissue selectivity. Proliferative or dysplastic epithelial cells prefer it since the compromised epidermal barrier prevents the absorption of exogenous ALA which in turn slows down the conversion of PpIX into haem[4].

Methylene blue and toluidine blue-O, two of the Ps that are used intraorally and are phenothiazinium salts from the synthetic dyes group that are most frequently used in dentistry and aPDT,these are some of the examples of non-toxic PSs[12] .

Additional PSs that have been proven safe and effective include Rose Bengal, nano-sized natural zeolite, natural chemicals like curcumin, and synthetic fluorescent dyes like Indocyanin[12]. A variety of PSs combined with nanoparticles have also been created, and their effectiveness and safety in clinical settings have been studied. adverse effects that should be taken into account while

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performing clinical research include prolonged skin sensitivity, localized tissue damage, and the possibility of skin and eye damage from excessive exposure to high intensity radiation and unpredictable efficacy[12].

LIGHT SOURCE :

Initially, the light sources for an aPDT were non-coherent light sources like conventional lamps. Because of their coherence and monochromaticity, two unique qualities, lasers are thought to be the perfect light source for APDT[5]."Low level laser therapy" (LLLT) is the term for the use of these lasers to treat soft tissue lesions[6].With the recent advancements in laser devices, such as semiconductor lasers like diode lasers (600-950 nm), argon lasers (448-514 nm), and solid-state lasers like Nd/YAG laser, lasers are preferred as the source of irradiation in aPDT[3]. Delivered by an optical fiber, monochromatic light can provide a more steady beam and make it simple to calculate light dosimetry and irradiation at the ideal wavelength for a certain photosensitizer[3].These days, diode lasers are often utilized in APDT clinics. They have a high energy conversion efficiency and are portable.These Laser gadgets are expensive, too. As an alternative, high-power LEDs, which produce coherent light as well, can serve as an APDT light source. In APDT, lamps including short-arc xenon lamps and metal halogen lamps are also utilized, particularly for the treatment of dermatological conditions. Since the wavelength bands of LEDs are broader than those of photosensitizers, heat is produced at the target region, which has a cytotoxic impact and destroys cells[4].

LEDs emit light with a wavelength ranging from 350 to 1100 nm. The gadgets' benefits include being less expensive and portable.The "therapeutic window" is the most important wavelength for aPDT which is approximately 600–800 nm[3]. A range of variables should be taken into account when determining light sources, including the lesion's attributes (tissue type, size, location, and accessibility), the photosensitizer (absorption spectrum and mode of administration), the light source's cost, and the device's availability. While many light doses may be employed in APDT to oral white lesions, the most frequently used dosage is 100 J•cm−2, which is strong enough for a 635–645 nm light source to induce ROS.

MECHANISM OF APDT

The manner in which APDT operates is that a photosensitizing agent is given topically or intravenously to the target tissue, and then a certain wavelength of light is irradiated there while oxygen is present. After being applied topically or intravenously, the photosensitizing agent accumulates within the target tissues that require treatment.[3] Their aberrant microvasculature and high proportion of low density lipoprotein (LDL) receptors in their cell membranes provided an explanation for this.[4] Yet, due to variations in the permeability of their external structures, bacteria, fungi, and other microbes also show selective accumulation of PSs, in addition to this kind of tissues. Furthermore, there is a selective buildup of PSs in a number of normal bodily tissues, while the precise cause is unknown.

This excited triplet state of photosensitizer undergoes two types of reactions: type I and type II reactions with the degree of potency depending on the concentration of Photosensitizing agents and the presence of oxygen[5] .

Type I reaction is an electron – transfer reactions between the excited photosensitizing agents and organic molecule of the tissues, producing free radicals. These free radical species are generally highly reactive in nature and easily react with endogenous oxygen molecules of the target tissues to produce reactive oxygen species, such as superoxide, hydroxyl radical etc, which are harmful to cell membrane integrity, causing target tissue destruction[5].

The second type is type II reaction in which the excited triplet-state Photosensitizing agent reacts directly with oxygen, which in turn generates singlet oxygen.Due to its high chemical reactivity, this singlet oxygen may readily interact with a wide range of biological substrates. In particular, its water content can cause oxidative damage, which can eventually lead to the disruption of cell membranes and the killing of target tissues[7].

In physiological systems, singlet oxygen has an extremely narrow radius of action (0.02 µm) and a short half-life. Because the oxidative process occurs in a small region and produces a confined response[4], it may be applied to targeted locations without harming other tissues or organs. It is acknowledged that the primary mechanism for the destruction of target tissue is the type II response.

APDT produces its effects to the target tissues by three mechanisms: cellular, vascular and immunological responses.The combination of these reactions is determined by the light sources being employed, the photosensitizer, and the availability

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of tissue oxygen[4]. Photosensitizers that are located in lysosomes and plasma membranes mostly cause necrosis-induced cell death, whereas those that are concentrated in mitochondria cause apoptosis-induced cell death[5]. It is desirable that they do not build up in the nucleus since there is a smaller possibility of DNA mutations occurring as a result. Because of potential changes in vessel diameter, platelet aggregation, and vascular leakage[4] during therapy, APDT may result in the production of edema. This results in indirect harm by lowering the concentration of nutrients and oxygen, which in turn compromises the efficacy of APDT. PDT cannot be induced in the absence of oxygen and singlet oxygen.

Also APDT affects the immune system and cytokines, chemokines etc are released.The inflammatory cytokines IL-6 and IL-10 are regulated after APDT. Also, neutrophils were increased innumber after PDT[4]

Clinical procedures

PREOPERATIVE CARE

Any patient with oral white lesions, including those who have had recurrence following cryotherapy, laser ablation therapy or surgical excision, can benefit from APDT as a therapeutic option[4]. When it comes to some oral white premalignant lesions like erythro-leukoplakia and oral verrucous hyperplasia, APDT has been suggested as one of the best treatment choice. Nonetheless, a complete medical history of the patient must be obtained. Treatment with APDT may not be appropriate for a patient with a history of porphyria, blood coagulation disorder, pregnancy, uncontrolled severe systemic disorders like uncontrolled hypertension, diabetes, heart disease, severe liver and kidney damage, or malignant tumors, as well as any history of photosensitivity, allergy to porphyrin, or use of anesthetic agents[4].

Biopsy should be taken from the target lesion to determine the degree of dysplasia and whether there is presence of inflammation or not. Also it is essential to note the clinical and histopathological characteristics of the patients, including age,sex, personal and family history, size and type of the lesion[4] . For the purpose of the patient's case history record, pictures of the lesions have to be captured and saved. In order for patients to fully understand the treatment objective, treatment plan, potential results, and potential adverse reactions, the doctor should discuss with them the various treatment options, along with the benefits and drawbacks based on the operating techniques, indications, and contraindications of APDT[4].

In order to have surgery, the patient must give consent in writing, attesting to their complete knowledge of the procedure's goals, course of action, potential outcomes, potential side effects, and preventative measures. Before the operation, it is also advisable to assess the total blood cell counts, glucose level, blood coagulation time, and liver and kidney function, among other blood indices[4].

In addition to helping with the operation, the nursing staff is in charge of getting the supplies ready for APDT and meticulously verifying the patient's name, sex, case file, diagnosis, and target lesion, among other details. Patients who are exhausted or have an empty stomach should not get treatment[4].

The treatment room should have a tight light-proof environment since APDT should be done in a dark room. External light interference will be reduced by curtains made of double-layered blackout material with high light-shielding properties[4].Before the process, treatment-related materials such the photosensitizer (ALA), the APDT device's settings and optical fibres as well as other materials, such as examination trays, disposable mouthwash glasses, disposable syringes, local anaesthetics solution, sterile cotton rolls and balls, disinfection appliances, goggles, sterile isolation films, 0.1% chlorohexidine mouthwash, and medical swabs etc. should be double verified.[4]

POST-OPERATIVE CARE

The patient should be instructed to avoid foods and beverages that could irritate their oral mucosa, to keep their mouth clean, and to practice good oral hygiene[4]. In addition, light exposure should be avoided for 48 hours following APDT therapy in the affected region. This protection from light should be extended to last the full course of therapy if the lesion is situated in an exposed area.[4]

In addition to asking patients to report any negative responses to the medical staff, post-treatment pain should be measured using a visual analogue scale. Following therapy, topical 0.1% chlorohexidine mouthwash solution and 0.01% dexamethasone paste are often administered to decrease inflammation[4].

Usually, four weeks following the most recent therapy, the therapeutic response is documented. The lesion response is designated a

Complete Response (C): if the visible lesion disappears.

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Partial Response (P): if a reduction in size of minimum 20% occurs
No Response (N): If A Reduction In Size Of less thjan 20% Or An Increase In Size Occurs[4].
The total response (T) rate was calculated using the following formula: T=(C+P)/(C+N+P)×100

ADVERSE EFFECTS:

Mild to moderate pain is the most frequent adverse response after APDT for oral white lesion. among others, elevated blood sugar, edema, Bleeding, ulceration etc in the treated region as well as in the tissues around it[3]. Severe cases can be treated with topical prednisolone solution, and anti-inflammatory and antiseptic medications, such as 0.1% chlorohexidine mouthwash solution[9], to lessen symptoms. Mild cases, on the other hand, can heal on their own. Benzocaine gel or lignocaine cream can also be administered topically for really painful cases. Oral prednisone acetate tablets can be used for a short period of time (3–5 days) and at a modest dose (15–30 mg) in situations with more severe erosion and ulceration[9]

Another extremely typical adverse effect of the therapy is light sensitivity, which shows up as ulcerations, blisters, papules, and maculae on the APDT-treated region when exposed to bright indoor or outdoor light[4]. Patients should avoid direct sunlight or indoor light exposure on the APDT-treated region and, if required, use protective gears to avoid such responses[4].Treatment options include removing the patient from the lighted area as soon as possible and getting medical help, taking oral antihistamines like cetirizine, gargling with anti-inflammatory medications like 0.1% chlorohexidine, applying glucocorticoid preparations, like prednisolone solution, dressing the lesion topically, and seeing a dermatologist right away if skin damage develops[4].

ADVANTAGES:

- Accurately and precisely target diseased areas
-Painless and non-invasive technique.
-Avert the emergence of bacterial resistance.
-Minimize bleeding and swelling.
-Target harmful microbes specifically while avoiding harm to healthy cells.

DISADVANTAGES:

- Higher cost than usual therapy;
- specific training required;
- sensitivity to light for several days or weeks following treatment

II. DISCUSSION:

APDT, a minimally invasive technique, has emerged as an alternative therapeutic modality for the treatment of oral white lesions, in addition to conventional surgery, CO2 laser ablation, and cryosurgery etc. This is due to its efficacy and low risk of systemic side effects, which have been enhanced by recent advancements in photosensitizers and light delivery systems. Large and recurring lesions can be treated with this method, which has few long-term effects on patients. It is easy to use, suitable for most dental clinics, and appreciated by patients[4].

On the other hand, there are still lack of information known on the effectiveness of APDT in treating oral white lesions. Before more comprehensive guidelines for the care of oral white lesions are developed, studies with standardized parameters and methods, randomized clinical trials at several areas with sufficient sample numbers, and intermediate and long-term follow-up periods are required[4]. More research should focus on the following areas like how APDT affects malignant transformation; how to increase APDT's effectiveness in treating oral white lesions etc.

III. CONCLUSION:

Comparing the clinical research has led to the primary conclusion that APDT is a safe and efficient advanced therapy option for oral white lesions. The majority of studies showed a substantial reduction in the signs and symptoms of oral white lesions as well as an increase in symptom-free times, demonstrating the exceptional effectiveness and improvement evidences of APDT in treating oral white lesions[3,4]. We were unable to provide conclusive evidence for the benefit of APDT in the treatment of oral white lesions due to the little number of pertinent published data on the procedure, small sample size, and brief follow-up periods[4,8,9]. To assess APDT's efficacy in treating oral white lesions, further clinical research, verifications using randomized clinical trials, a bigger patient population, and extended follow-up times are required.

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